Medicines Adverse Reactions Committee

Meeting date	13/06/2019	Agenda item	3.2.3
Title	**Fluoroquinolones and aortic aneurysm or dissection**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Ciprofloxacin	Ciproxin oral suspension	Bayer
	Cipflox tablet, infusion	Mylan
	Ciprofloxacin tablet (Rex)	REX Medical
	Aspen Ciprofloxacin injection	Pharmacy Retailing
	Ciprofloxacin infusion (AFT)	AFT
Moxifloxacin	Avelox tablet, infusion	Bayer
Norfloxacin	Arrow - Norfloxacin tablet	Teva Pharma

PHARMAC funding	Cipflox, Avelox and Arrow-Norfloxacin
Previous MARC meetings	Disabling and persistent musculoskeletal and nervous system adverse reactions from the use of fluoroquinolones were discussed at the 7 December 2017 MARC-meeting.
International action	See section 3.2
Prescriber Update	Quinolones – A Tendoncy to Rupture (September 2012)
Classification	Prescription medicine
Usage data	See section 2.1.5
Advice sought	**The Committee is asked to advise whether:** • The data sheets should be updated regarding the risk of aortic aneurysm and dissection • The indications for fluoroquinolones should be restricted. • This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

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1   PURPOSE

Medsafe was alerted to a published study in 2018 on potential risk of aortic aneurysm and dissection in association with use of fluoroquinolones (1). At the same time, the topic was under review by the FDA and PRAC, and their reviews are now complete. The conclusions by both FDA and PRAC was to recommend updates of the product information with a warning. Updates have also been requested in Singapore and Switzerland. Australia and Canada are in the process of assessing the issue.

The purpose of this paper is to review available information, focusing on oral and parenteral fluoroquinolone use. Considering the severity of the potential adverse reactions and the use of fluoroquinolones in New Zealand, Medsafe considers that these safety concerns should be referred to the MARC for their advice as to whether data sheets and recommendations should be updated.

This paper also provides an update on regulatory activities regarding the risk of disabling and persistent musculoskeletal and nervous system adverse reactions in relation to treatment with fluoroquinolones, which was previously discussed at the December 2017 MARC meeting (see section 3.2.2).

Following the safety concerns described above, some regulatory agencies have decided to restrict the indications for fluoroquinolones. Medsafe is requesting advice from the MARC whether the indications in NZ should be restricted. This issue is discussed in section 3.2.3.

2   BACKGROUND

2.1   Fluoroquinolones

Fluoroquinolones are used for a variety of infections, especially against aerobic gram-negative bacteria. The first of the synthetic quinolones, nalidixic acid, was discovered in 1962. Later, a fluorine atom was added to the quinolones and they became fluoroquinolones. A piperazine ring was also added and in both cases, the purpose was to make the medicines more effective.

Three fluoroquinolone antibiotics are available in New Zealand: ciprofloxacin, norfloxacin and moxifloxacin.

Fluoroquinolones can be classified into different generations, although which generation each of them belong to tend to differ depending of source of information used. According to the European Surveillance of Antimicrobial Consumption (ESAC) classification, norfloxacin is a first generation fluoroquinolone, ciprofloxacin is second generation, while moxiflocacin belongs to the third generation (2).

Newer fluoroquinolones have a broader spectrum of activity including better coverage of gram-positive organisms and, for some of them, anaerobes.

2.1.1   Indications

Table 1 lists the approved indications of ciprofloxacin, moxifloxacin and norfloxacin in NZ.

Table 1. Therapeutic indications (3-5).

Fluoroquinolone	Indications
Ciprofloxacin	Adults: Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens in the: - lower respiratory tract In the treatment of outpatients with pneumonia due to *Pneumococcus*, ciprofloxacin should not be used as a medicine of first choice. Ciprofloxacin can be regarded as a suitable treatment for pneumonias caused by *Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Branhamella, Legionella, and Staphylococcus.* - kidneys and/or the efferent urinary tract - genital organs, including adnexitis, gonorrhoea, prostatitis - abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis) - skin and soft tissue. - bones and joints. - sepsis. - inhalational anthrax (post-exposure) Listed pathogens that can be regarded as sensitive, have varying degree of sensitivity or are resistant. Prescribers are recommended to consider official and local guidelines. Children: - treatment of acute pulmonary exacerbation of cystic fibrosis associated with P. aeruginosa infection in paediatric patients aged 5-17 years - inhalational anthrax (post-exposure) - complicated urinary tract infections or pyelonephritis due to E.coli in paediatric patients aged 1 - 17 years. The risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints/surrounding tissues. The use of ciprofloxacin for other indications is not recommended in children.
Moxifloxacin	Tablets and solution for infusion are indicated for the treatment of the following bacterial infections caused by susceptible strains: - Bronchitis (acute exacerbations of chronic bronchitis) - Pneumonia (community acquired) - Sinusitis (acute) - Complicated skin and skin structure infections (including diabetic foot infections) - Complicated intra-abdominal infections including polymicrobial infections such as abscesses Tablets are indicated for the treatment of the following bacterial infections caused by susceptible strains:

	- Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis)
Norfloxacin	- upper and lower, complicated and uncomplicated acute urinary tract infections including cystitis, pyelitis, cystopyelitis, pyelonephritis, chronic prostatitis, epididymitis, and those urinary infections associated with urologic surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to norfloxacin - acute bacterial gastroenteritis caused by susceptible organisms - gonococcal urethritis pharyngitis, proctitis or cervicitis caused by both penicillinase and non-penicillinase producing Neisseria gonorrhoeae
	Infections caused by multiply-resistant organisms have been successfully treated with the usual doses of norfloxacin.

2.1.2   Dosing and duration of treatment

Ciproxin

The recommended dose and duration of treatment differ depending on indication. Daily doses vary between 250 and 1000 mg (1500 mg if particularly severe, life-threatening infection) orally and 100 – 1500 mg intravenously. Recommended duration of treatment is between 1 and 21 days, and up to two months for osteomyelitis and inhalational anthrax (post-exposure) (3).

Avelox

The recommended dose for Avelox is 400 mg once daily (1 film-coated tablet or 250 ml solution for infusion). Duration of treatment varies depending on indication, between 5 and 21 days (4).

Arrow-Norfloxacin

Recommended dose is 800 mg per day for 1-10 days (4 weeks for chronic prostatitis) (5).

2.1.3   Funding

Ciproflox tablets are currently funded by PHARMAC. In the Community section of the Pharmaceutical Schedule it is recommended for the following indications:

- microbiologically confirmed and clinically significant pseudomonas infection; or
- prostatitis; or
- pyelonephritis; or
- gonorrhoea

Arrow-Norfloxacin tablets are currently funded. However, in the community it is only funded if prescribed for a patient with an uncomplicated urinary tract infection that is unresponsive to a first line agent or with proven resistance to first line agents and the prescription is endorsed accordingly.

Avelox (moxifloxacin) tablets are funded with a Special Authority if prescribed by:

- A respiratory or infectious disease specialist for tuberculosis under certain circumstances.
- Any GP for confirmed and symptomatic Mycoplasma genitalium when the patient has tried and failed azithromycin or has confirmed azitroycin resistance. Maximum 7 days treatment.
- An ophthalmologist if the patient requires prophylaxis following a penetrating eye injury and treatment is for 5 days only.

Comment: The therapeutic indications and the funding of moxifloxacin do not match.

2.1.4   Pharmacodynamics

Fluoroquinolones act as direct inhibitors of bacterial DNA synthesis. Two bacterial enzymes, DNA gyrase and topoisomerase IV, which have essential and distinct roles in DNA replication are inhibited by fluoroquinolones. The quinolones bind to the complex of each of these enzymes with DNA. The resulting complexes, including the medicine, block progress of the DNA replication enzyme complex. Ultimately, this action results in damage to bacterial DNA and bacterial cell death (6).

2.1.5   Pharmacokinetics

The quinolones are well absorbed from the upper gastrointestinal tract. Peak concentrations in serum are usually attained within one to three hours of administering an oral dose and the volumes of distribution of are large.

The terminal elimination half-lives from serum range from three hours for norfloxacin, and ciprofloxacin to six to eight hours for moxifloxacin.

Ciprofloxacin and norfloxacin have mixed excretion by both renal and nonrenal routes. Renal clearance of norfloxacin and ciprofloxacin exceeds glomerular filtration rates (GFR), indicating net tubular secretion. Hepatic conversion of norfloxacin and ciprofloxacin to less active metabolites accounts for 10 to 20 percent of elimination. For moxifloxacin, the principal routes of elimination are hepatic metabolism and biliary excretion (6).

2.1.6   Adverse effects

Fluoroquinolones, as a class, are generally well tolerated. Most adverse effects are mild in severity, self-limiting and rarely result in treatment discontinuation (7). Adverse reactions commonly associated with fluoroquinolones are shown in Table 2:

Table 2.

Adverse reaction	Range of incidence (%)
Gastrointestinal (diarrhoea, vomiting)	0.8 - 6.8
Central nervous system (dizziness, headache)	0.9 – 11
Skin (rashes)	0.4 - 2.1
Blood disorders	0.5 - 5.3
Cardiovascular (palpitations)	0.5 - 2.0
Musculoskeletal	0.5 - 2.0
Phototoxicity or photoallergy	0.5 - 2.1
Serious reactions, eg, haemolytic uremic syndrome, Stevens Johnson syndrome	<0.5

Rare occurrences of convulsions and psychosis have been reported. Rupture of tendons or tendonitis is a rare event associated with fluoroquinolones. Such events tend to affect the Achilles tendon, and are bilateral in 50% of cases. Predisposing factors include corticosteroid therapy (especially in the elderly), renal disease, haemodialysis and transplantation. Another risk group for tendon rupture as well as other musculoskeletal complications has been reported to be athletes in training (8).

As discussed at the December 2017 MARC-meeting, fluoroquinolones have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system and musculoskeletal system.

With the identification of adverse events associated with some fluoroquinolones, newer fluoroquinolones have been scrutinised closely because of class-related adverse effects. Several of the newer fluoroquinolones have either been withdrawn from the market or had their use severely restricted because of adverse effects.

Aortic aneurysm and dissection are not listed as adverse reactions in the data sheets of the fluoroquinolones available in NZ.

2.1.7 Recommendations for use from other organisations

According to the NZ Formulary (9), norfloxacin is effective in uncomplicated urinary-tract infections but should be reserved for isolates resistant to empiric choices (trimethoprim or nitrofurantoin) and avoided in pregnancy.

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae;* it should not be used for pneumococcal pneumonia. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, and septicaemia caused by sensitive organisms. It may also be used in the treatment of multi-drug resistant *Streptococcus pneumoniae*. Many staphylococci are resistant to the quinolones and their use should be avoided in staphylococcus infections, including skin and soft tissue infections.

Moxifloxacin should be reserved for the treatment of community-acquired pneumonia, which has failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials and as a second-line treatment for tuberculosis. Moxifloxacin is active against Gram-positive and Gram-negative organisms. Compared to ciprofloxacin, moxifloxacin has poorer activity against *Pseudomonas aeruginosa*.

The Best Practice Advocacy Centre (BPAC) states that fluoroquinolones should be reserved for serious bacterial infections, and used only when there is no practical alternative (10). There are very few situations in general practice where a quinolone would be considered first-line treatment.

2.1.8 Usage data

Usage data for oral fluoroquinolones are shown in Table 3.

Table 3. Number of fluoroquinolone dispensings and number of people receiving a dispensing at least once during the year at community pharmacies

Year	Ciprofloxacin		Moxifloxacin		Norfloxacin	
	Dispensings	Nb of people	Dispensings	Nb of people	Dispensings	Nb of people
2014	86,990	63,879	371	105	48,696	35,667
2015	84,180	62,476	352	133	21,111	15,275
2016	82,880	62,111	298	111	16,680	11,878
2017	78,462	59,145	467	218	12,030	8,416
2018	69,976	52,941	485	246	11,941	8,375

Source: MoH Pharmaceutical Collection (Data Pharm), extracted 26 March 2019

Figure 1 shows how many patients received a dispensing of at least one flouroquinolone by different age-groups, comparing years 2013 and 2018.

Figure 1.

Number of patients in different age groups who were
dispensed at least one fluoroquinolone in 2013 or 2018
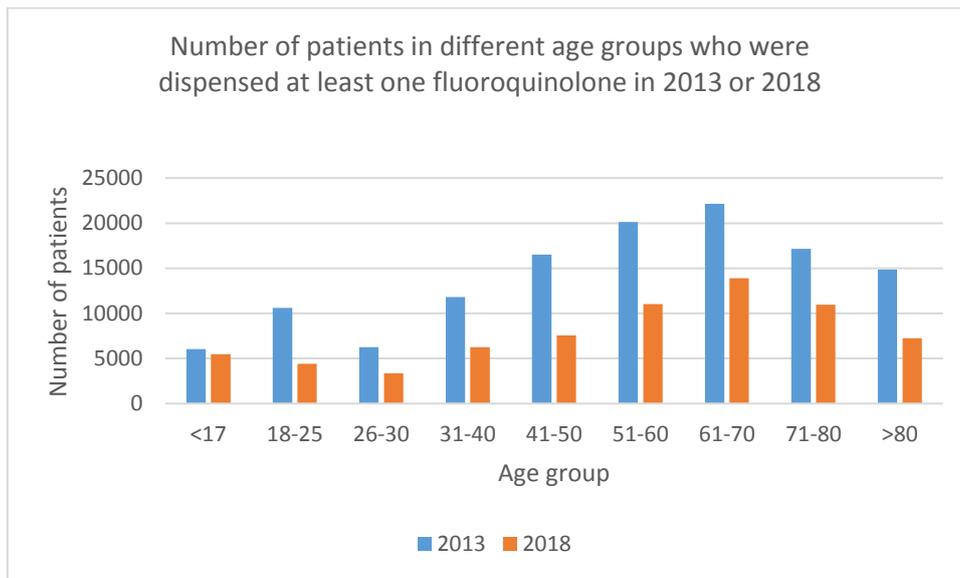
Source: Pharmaceutical Collection, extracted 15 April 2019

Figure 2 shows how many patients in different age-groups received a dispensing of moxifloxacin in year 2013 and 2018.

Figure 2.

Number of patients in different age groups who were
dispensed moxifloxacin in 2013 or 2018
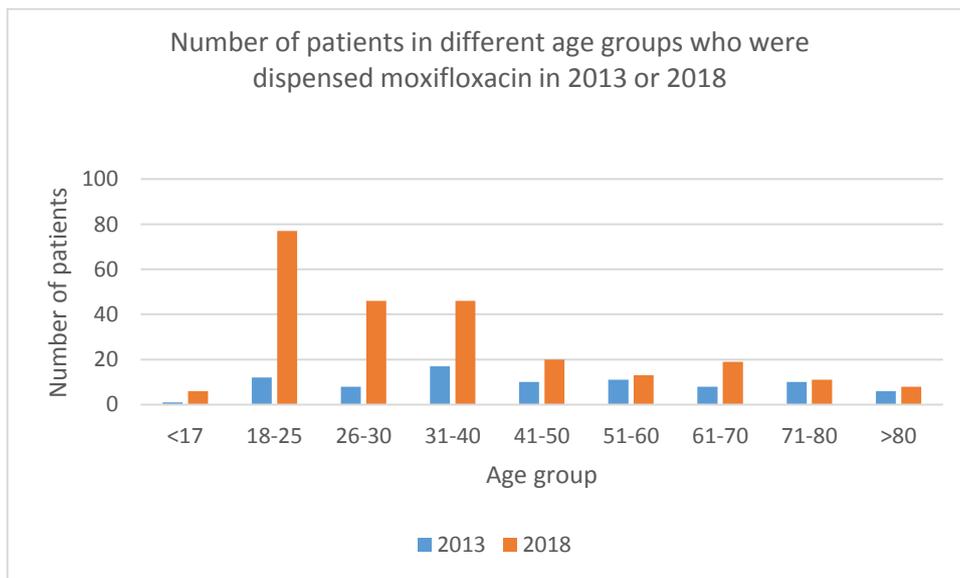
Figure 3a and b illustrates how many patients over 65 years of age who received a dispensing of ciprofloxacin, norfloxacin and moxifloxacin respectively.

Figure 3 a, b.

Number of patients >65 years who were dispensed ciprofloxacin or norfloxacin

Number of patients >65 years who were dispensed moxifloxacin
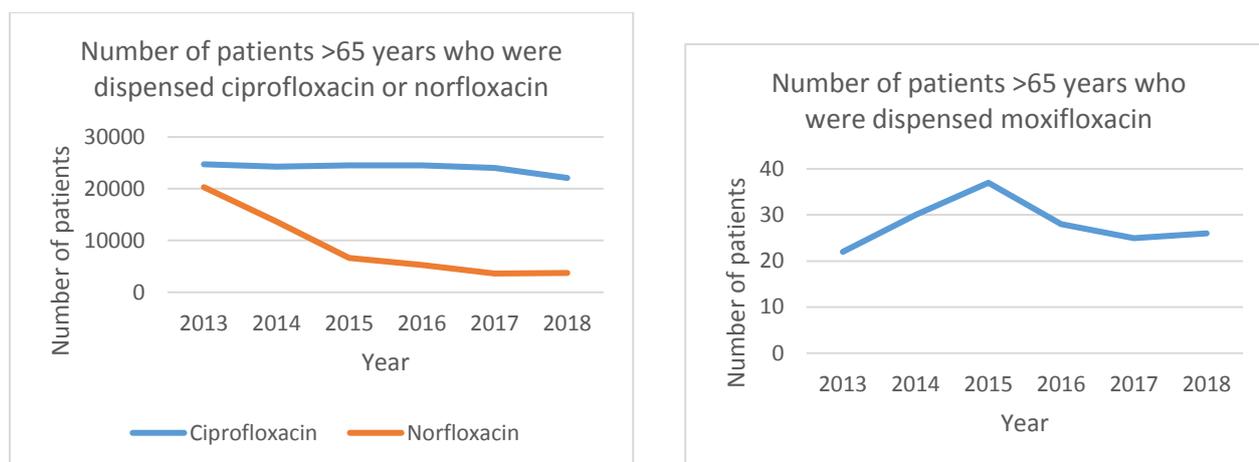
Comments: Dispensing data indicates that the use of ciprofloxacin and norfloxacin are decreasing but use of moxifloxacin is increasing, in all age-groups. This is of concern as community prescribing of quinolones significantly contributes to antimicrobial resistance. Some of these prescriptions may however be for patients just leaving the hospital. In the age group over 65 years, norfloxacin prescribing is decreasing but for ciprofloxacin and moxifloxacin prescribing is relatively stable with moxifloxacin slightly on the rise.

2.1.9 Resistance to fluoroquinolones

Due to the extensive use of fluoroquinolones in human and veterinary medicine, and despite prescribing guidelines recommending reserving quinolone use, the number of quinolone-resistant strains has been growing steadily worldwide, being observed in all species treated by this antimicrobial class. Although still clinically valuable, quinolone use has been compromised by the emergence of resistance, having serious implications in some clinical settings. Several mechanisms of resistance have been described:

- chromosomal mutations altering the target enzymes and their drug-binding affinity.
- chromosomal mutations leading to reduced drug accumulation by either decreased uptake or increased efflux.
- plasmid-acquired resistance genes producing either target protection proteins, drug modifying enzymes or drug efflux pumps (11).

The cellular alterations associated with each mechanism can accumulate to create highly resistant strains and plasmid-encoded resistance genes promote selection of higher-level resistance mutations. Plasmid-mediated mechanisms are almost always associated with resistance to other antibiotics.

Antimicrobial susceptibility data generated from routine diagnostic susceptibility testing in hospital and community microbiology laboratories in NZ from the Institute of Environmental Science and Research Ltd (ESR) are shown in table 4 (12).

Table 4: Antimicrobial susceptibility data from hospital and community laboratories for year 2016 and 2017: percent susceptible (number tested) for fluoroquinolones.

	Percent susceptible to fluoroquinolones (numbers tested)	
	2016	**2017**
Acinetobacter calcoaceticus-baumannii complex	95.5 (267)	93.6 (215)
Enterobacter species from bacteraemia	97.7 (172)	98.1 (157)
Escherichia coli (non-ESBL) from bacteraemia	93.5 (1650)	91.5 (2181)
Escherichia coli (ESBL) from bacteraemia	41.5 (142)	35.6 (225)
E.coli (non-ESBL) urinary	93 (65300)	90.8 (79003)
E.coli (ESBL) urinary	37.4 (2917)	32.7 (3627)
Klebsiella species (non-ESBL) from bacteraemia	96.3 (382)	94 (382)
Klebsiella species (ESBL) from bacteraemia	33.3 (60)	21.2 (33)
Pseudomonas aeruginosa from bacteraemia	93.6 (219)	90.5 (231)
Methicillin-susceptible Staphylococcus aureus from bacteraemia	97.8 (732)	98.8 (854)
Methicillin-resistant S. aureus from bacteraemia	89.3 (112)	90.3 (113)
Methicillin-susceptible S. aureus from skin and soft tissue infection	97.2 (26882)	97.3 (24007)
Methicillin-resistant S. aureus from skin and soft tissue infection	87.1 (8133)	87 (7929)

Results from previous years for fluoroquinolones are shown in the table below**.** Note that the data for years prior to 2016 is presented as rates of resistance whereas data for the years 2016 onwards is presented as rates of susceptibility (12).

Table 5. Antimicrobial resistance data from hospital and community laboratories: percent resistance (number tested).

	Acinetobacter species	Citrobacter freundi	Enterobacter species	Escherichia coli from bacteraemia	E. coli urinary	Klebsiella species from bacteraemia	Morganella morganii	Proteus mirabilis	Pseudomonas aeruginosa	Serratia species
2010	4.2 (595)	3.1 (388)	2.9 (2544)	9.7 (1708)	6.2 (75217)	9 (387)	5 (561)	1.1 (2654)	6.6 (12567)	8.6 (973)
2015	4.0 (550)	4.2 (336)	2.1 (2327)	10.2 (1572)	8.5 (73788)	11 (337)	8.7 (909)	2.9 (2741)	7 (9491)	6.7 (1167)

Comments: There is increasing resistance to quinolones in New Zealand, which should be taken into account when prescribing the medicines.

2.2   Aortic aneurysm and dissection

2.2.1   Clinical features

Both aortic aneurysm and dissection are very severe conditions with high mortality.

Aortic aneurysm

An aortic aneurysm is a bulging, weakened area in the wall of the aorta. Over time, the blood vessel balloons and is at risk for bursting (rupture). This can cause life threatening bleeding and potentially death. Often, aortic aneurysms grow slowly and cause no symptoms until they rupture, a catastrophic event associated with an estimated mortality rate of over 80%.

Aortic aneurysms can happen anywhere along the length of the aorta, but they are most common in the lower part, a so called abdominal aortic aneurysm. Thoracic aortic aneurysms are located in the upper part of the aorta, in the chest.

The known risk factors for aortic aneurysm development include age, smoking, hypertension, genetic factors and Marfan's syndrome (a genetic condition associated with a weakened and enlarged aorta).

Once formed, an aneurysm will gradually increase in size over time and get progressively weaker. Treatment for a thoracic aneurysm may include surgical repair or removal of the aneurysm, or inserting a metal mesh coil (stent) to support the blood vessel and prevent rupture (13).

Aortic dissection

An aortic dissection is a serious condition in which the inner layer of the aorta, the large blood vessel branching off the heart, tears. Blood surges through the tear, causing the inner and middle layers of the aorta to separate (dissect). If the blood-filled channel ruptures through the outside aortic wall, aortic dissection is often fatal. Onset is often sudden with severe chest or back pain.

An aortic dissection occurs in a weakened area of the aortic wall. Chronic high blood pressure may stress the aortic tissue, making it more susceptible to tearing. Marfan syndrome, bicuspid aortic valve or other rarer conditions associated with weakening of the walls of the blood vessels are other risk factors. Rarely, aortic dissections are caused by traumatic injury to the chest area, such as during motor vehicle accidents (14).

Dissection is classified according to whether it includes the ascending aorta (type A) or not (type B) (see Figure 4). Type A dissection is a surgical emergency because of the high risk of proximal extension, rupture, and sudden death. If a type A dissection is confirmed by CT or MRI, the patient should be operated on immediately. In contrast, type B dissection is managed medically by aggressive antihypertensive treatment (15).

Figure 4. Classification of dissection.
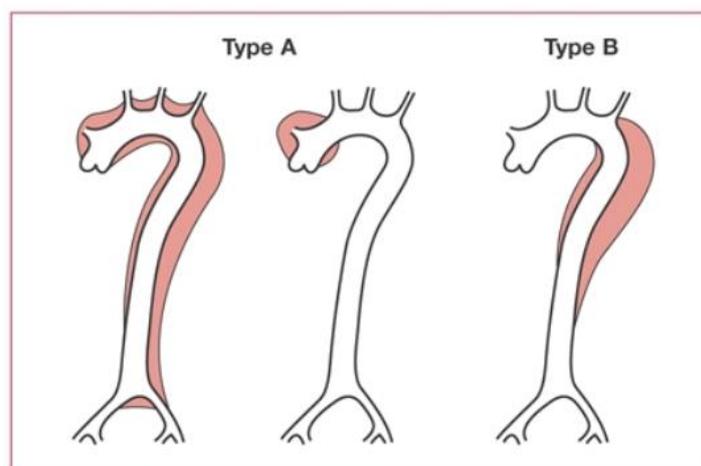
2.2.2 Epidemiology

Aortic aneurysm and dissection are relatively rare conditions. It is difficult to assess the prevalence and incidence of thoracic aortic aneurysm because it is a clinically silent disease. Fatalities due to thoracic aortic aneurysm complications (rupture, dissection) are likely to be attributed to other causes. The background risk also varies widely depending on the population at risk.

In a Swedish population–based cohort study of more than 14,000 cases from 1987 to 2002, the incidence of thoracic aortic disease (aneurysm and dissection) was noted to be 16.3/100,000 per year for men and 9.1/100,000 per year for women (16).

In the study by Lee 2018 below it is estimated an annual incidence of AA of 3 to 13.7 per 100,000 population, and AD of 3 to 20 per 100,000 population while the annual incidence of AA for the elderly population is reported to be much higher at 130 per 100,000 population.

An epidemiological study from 2015 gives an estimate of the annual risk for aortic aneurysm that ranges from nine aortic aneurysm events per 100,000 persons in a general population to 300 aortic aneurysm events per 100,000 persons at the highest risk (e.g., persons over the age of 85 years)(17).

2.2.3 Suggested mechanisms as to how fluoroquinolones could cause aortic aneurysm and dissection

While the exact mechanism of fluoroquinolone-induced aortic aneurysm or dissection is unknown, several possibilities have been proposed. Fluoroquinolone-associated tendinitis and tendon rupture are widely recognized complications of fluoroquinolone treatment.

The hypothesized biological mechanisms are thought to be that fluoroquinolones possess chelating properties against several metal ions (e.g., calcium, magnesium, aluminium), and have been known to cause direct toxicity to type I collagen synthesis and promote collagen degradation by inducing matrix metalloproteinase. Matrix metalloproteinases have been known to play a role in the pathogenesis of aortic aneurysms, whereas matrix metalloproteinase inhibitors may oppose the development of aneurysms.

Type I and type III collagen comprise the majority of collagen in the Achilles tendon, and also comprise the majority (80–90%) of collagen in the aorta, thereby suggesting that fluoroquinolones destroy collagen along the aortic wall leading to aortic aneurysm or dissection as they do on tendons. Pathological sections of aortic aneurysms and dissections demonstrate abnormalities of collagen content, concentrations and ratios. (18, 19). A study examining the interaction of fluoroquinolones with collagen from tendon cells demonstrated a significant increase in collagen dysfunction after fluoroquinolone exposure, likely because of changes in the regulation of matrix metalloproteinases (20).

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search resulted in 6 retrospective studies and 2 meta-analyses which are described below.

3.1.1 Pasternak B, Inghammar M, Svanström H, 2018, Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study (1)

This was a nationwide historical cohort study using linked register data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or dissection between July 2006 and December 2013. The aim was to investigate whether oral fluoroquinolone use is associated with an increased risk of aortic aneurysm or dissection.

Methods
The primary outcome was the risk of a first diagnosis of aortic aneurysm or dissection (admission to hospital or emergency department for aortic aneurysm or dissection, or death due to aortic aneurysm or dissection) associated with oral fluoroquinolone use, as compared with amoxicillin use, within a 60 day period from start

of treatment. To explore the timing of the association, the 60 day risk period was divided into 10 day intervals, assessing the number of events in each interval. A secondary analysis investigated the following 60 days. Amoxicillin was chosen as an active comparator because its approved indications overlap largely with those of fluoroquinolones, but there is no known association with aortic aneurysm or dissection.

The researchers used data from:

- National Prescribed Drug Register, which captures all prescriptions filled at all Swedish pharmacies since July 2005, including details pertaining to the specific drug and the date the prescription was filled.
- National Patient Register, which captures data for all hospital admissions and outpatient and emergency department visits in Sweden, including physician assigned diagnoses according to ICD-10 (international classification of diseases) as well as data for surgical procedures.
- Statistics Sweden, which captures data for demographic characteristics.
- Swedish Cause of Death Register.

The source population included all adults all adults in Sweden who received a prescription for fluoroquinolones or amoxicillin during the study and who were aged 50 years or older. This population was narrowed down according to Figure 5:

Figure 5.
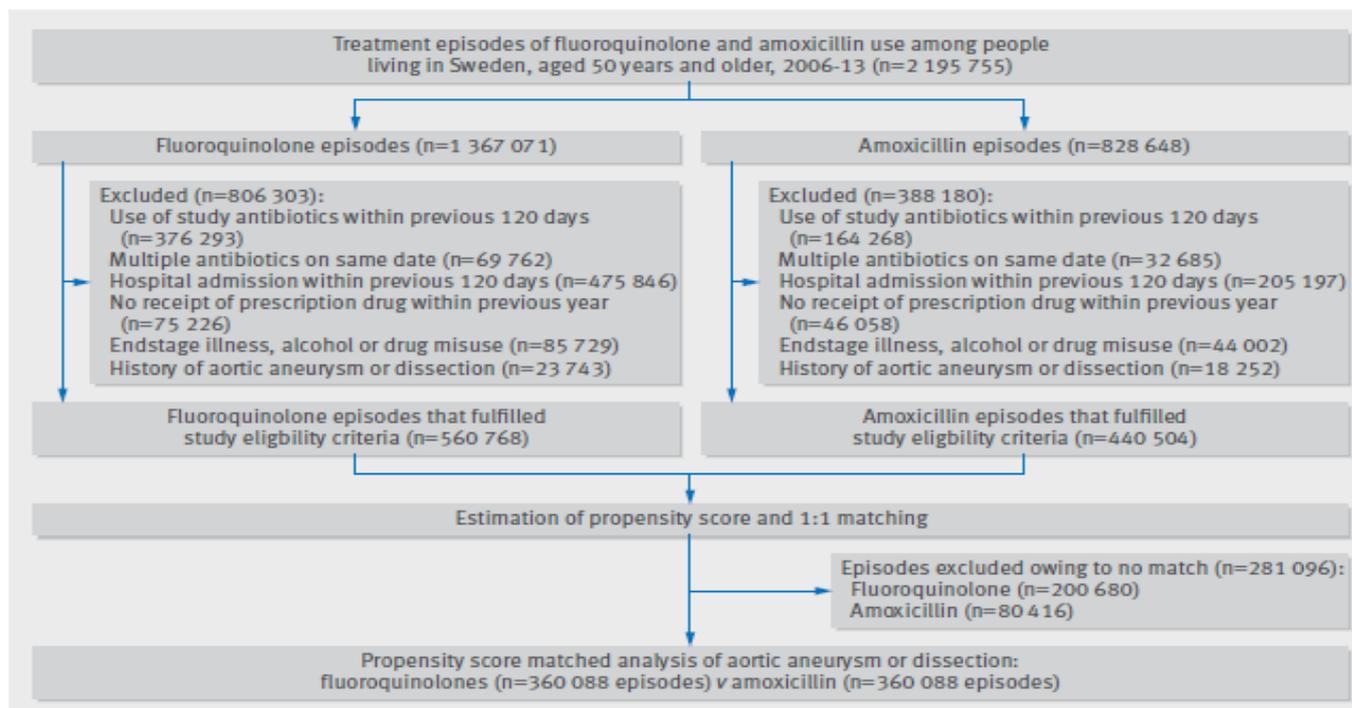
Fig 1 | Nationwide cohort of patients in Sweden with treatment episodes of fluoroquinolone use and amoxicillin use, 2006-13. Values for exclusion criteria do not add up to totals because some episodes were excluded for more than one reason

To control for potential confounding from differences in baseline health status, a propensity score matched design was used. The propensity score for fluoroquinolone exposure was estimated by a logistic regression model, including 47 covariates as predictors, covering demographic information, medical history, prescription drug use and healthcare use.

Results

The mean follow-up in the 60 day risk period was 52 days in the fluoroquinolone group and 55 days (14) in the amoxicillin group. In the group of fluoroquinolone users, 78% were prescribed ciprofloxacin. Among

360 088 treatment episodes of fluoroquinolone use, there were 64 cases of aortic aneurysm or dissection (incidence 1.2 per 1000 person years), compared with 40 cases among 360 088 treatment episodes of amoxicillin use (0.7 per 1000 person years). The cumulative incidence of aortic aneurysm or dissection at 60 days was 2.0×10^{-4} for episodes of fluoroquinolone use and 1.2×10^{-4} for episodes of amoxicillin use, see Figure 6:
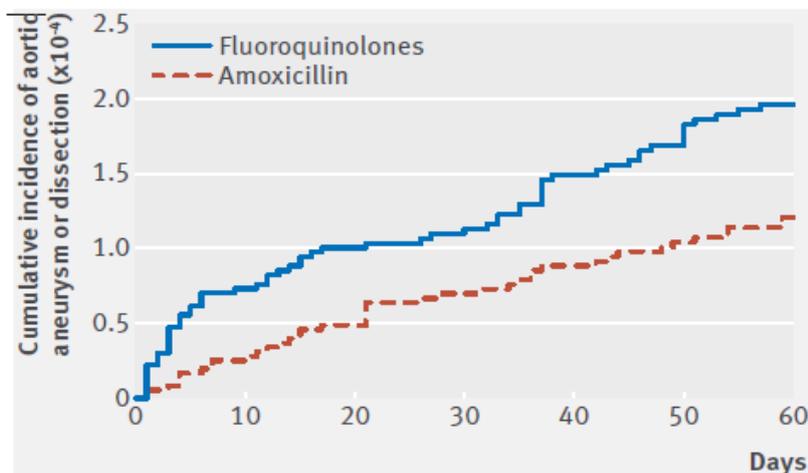
Fig 6. Cumulative incidence of aortic aneurysm or dissection within 60 day risk period from start of study treatment

Fluoroquinolone use was significantly associated with an increased risk of aortic aneurysm or dissection (HR 1.66; 95% CI 1.12 to 2.46), with an estimated absolute difference of 82 (95% CI, 15 to 181) cases of aortic aneurysm or dissection per 1 million treatment episodes.

In a secondary analysis, there was no increased risk of aortic aneurysm or dissection associated with fluoroquinolone exposure in the period of 61-120 days from start of treatment. If the 60 day risk period was divided into 10 day intervals to explore the timing of the association, 26 (41%) of the 64 cases of aortic aneurysm among patients treated with fluoroquinolones occurred in the first 10 days from start of treatment.

The hazard ratio for the association with fluoroquinolone use was 1.90 (95% confidence interval 1.22 to 2.96) for aortic aneurysm and 0.93 (0.38 to 2.29) for aortic dissection. Of the cases of aortic aneurysm or dissection that occurred among fluoroquinolone users, most were abdominal aneurysm, followed by thoracic or thoracoabdominal aneurysm.

> **Comments:** A strength with this study is that it uses an active comparator and also different strategies to control for confounding. The results support the notion that there may be a link between fluoroquinolones and especially aortic aneurysm, however the absolute risk in the study is small (an additional 82 incidents per million treatment episodes). The results were driven by aortic aneurysm - note that the hazard rate for aortic dissection was <1. The risk for aortic rupture was not linked to prolonged duration of therapy as 41% of cases of aortic rupture occurred in the first 10 days of quinolone treatment.

3.1.2   Lee CC, Lee MG, Hsieh R et al, 2018, Oral fluoroquinolone and the risk of aortic dissection (21)

The aim of this study was to evaluate the potential association between fluoroquinolone treatment and aortic aneurysm and dissection (AA/AD) via a case-crossover analysis and case-time-control study using data from a large national administrative database in Taiwan.

Methods
All inpatients diagnosed with AA or AD from 2000 to 2011 were identified. In the case-crossover part, the participants acted as their own controls, providing information on the outcome risk during exposed and

unexposed states. In the primary analysis, each case contributed 1 hazard period, 1 washout period, and 3 referent periods. The length of each period is 60 days. See figure 7:

Figure 7: Case-cross-over design
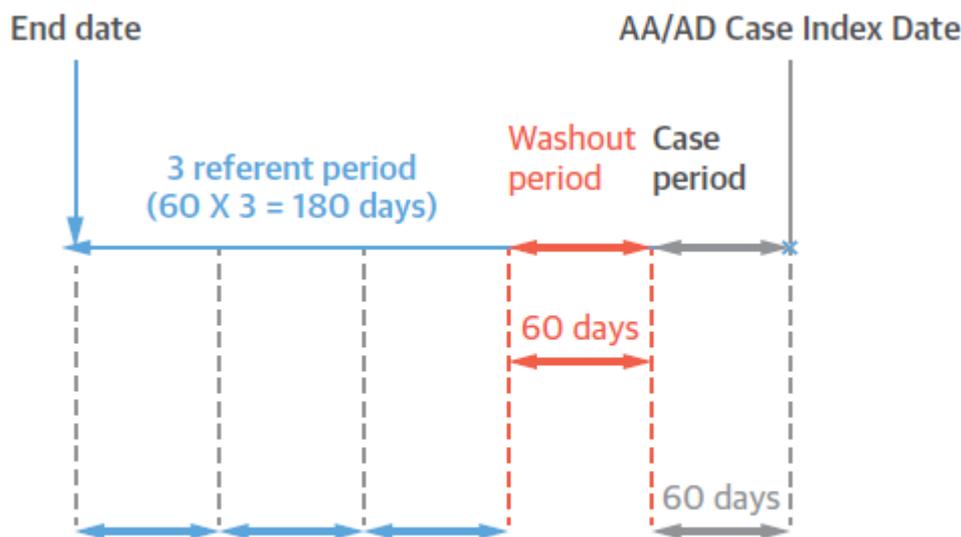
The distributions of fluoroquinolone exposure for a patient across a 60-day period before the AA/AD event (hazard period) were compared to 1 randomly selected 60-day period (referent period) between 60 to 180 days before the AA/AD events for the same patient. In the sensitivity analysis, the authors repeated the mainanalysis using a 1:5 ratio of hazard period to referent period, to adjust for the effect of time-variant confounders.

To adjust for potential exposure trend bias (for example if a spurious association between fluoroquinolone use and AA/AD is observed in a case-crossover analysis, but the real reason is that the use of fluoroquinolones has increased over time in the cases group or in the general population) the authors used a DRS (disease risk score) matched case-time-control design. The case-time-control design meant that the participants acted as their own controls but were also compared with a sample of appropriate controls. The exposure trend measured in the controls was used to adjust for the exposure-outcome association derived from case-crossover analyses.

To ensure that the selected group of controls was appropriate, they were selected using a DRS matching process (Figure 1B). Each case in the case-crossover analysis was matched 1:1 to the controls selected by DRS. The DRS was defined as the predicted probability of developing AA/AD among participants not exposed to fluoroquinolones. See figure 8:

Figure 8: DRS-matched study design
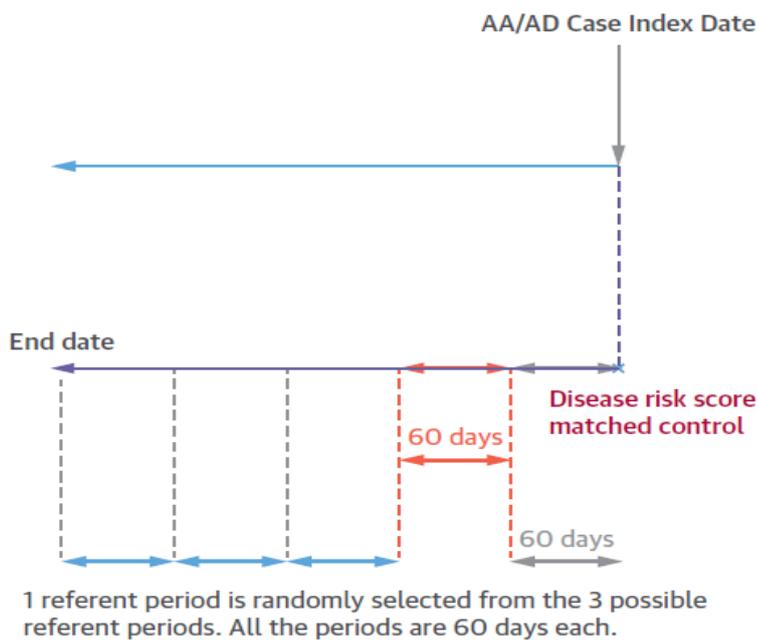
Exposure to fluoroquinolones was defined as a prescription length of 3 days or more.

Results

A total of 1,213 patients with AA/AD fulfilled the eligibility criteria. The majority of the AA/AD patients were male, elderly, and had a high prevalence of cardiovascular diseases related to AA/AD. Figure 9 illustrates the flow chart of the main analysis.

Figure 9.

Flow Chart of Cohort Selection in the Main Analysis
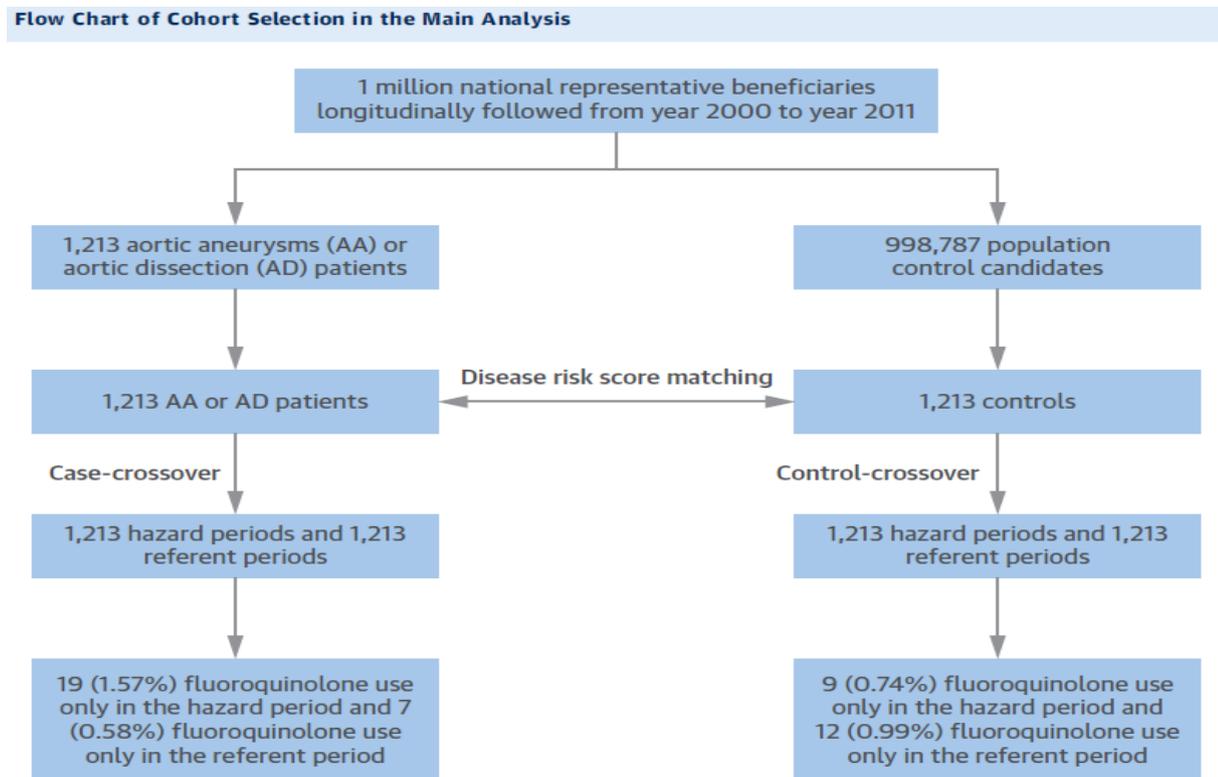
Main results:

- In the main case-crossover analysis, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.6% vs. 0.6%; odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.14 to 6.46).
- In the sensitivity analysis, after adjustment for infections and co-medications, the risk remains significant (OR: 2.05; 95% CI: 1.13 to 3.71).
- An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR: 2.41 for 3- to 14-day exposure; OR: 2.83 for >14-day exposure).
- Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD.
- In the case-time-control analysis, there was no evidence that the observed association is due to temporal changes in fluoroquinolone exposure.

The authors calculated that assuming the population incidence of AA/AD in the fluoroquinolone naïve population to be 6/100,000 patient-years, for every 9,747 persons receiving fluoroquinolones for more than 3 days, 1 excess case of AA/AD would occur. This number is substantial considering the use of fluoroquinolones. Given a higher underlying risk of AA/AD in the elderly population (130/100,000 patient-years for patients >65 years of age), for every 516 persons receiving fluoroquinolones for more than 3 days, 1 excess case of AA/AD would happen.

Comment: The authors do not distinguish between aortic aneurysm and aortic dissection and also only mention aortic dissection in the title of the publication. An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones, but not longer than 60 days.

3.1.3 Lee CC, Lee MG, Chen YS et al, 2015, Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone (22)

A total of 1477 case patients and 147 700 matched control cases from Taiwan's National Health Insurance

Research Database (NHIRD) were observed from January 2000 to December 2011 from about 1 million individuals longitudinally observed. Case patients were defined as those hospitalized for aortic aneurysm or dissection. One hundred control patients were matched for each case based on age and sex.

Methods

Primary outcome measures were the first occurrence of aortic aneurysm or dissection requiring hospitalization during the follow-up period. In a sensitivity analysis, these criteria were combined with surgical procedures for aortic aneurysm or dissection.

Use of fluoroquinolone was defined as having a prescription filled for 3 days or longer:
- within 60 days of the index date – current use
- between 61 and 365 days prior to the index date – past use
- for 3 or more days any time during the 1-year period before the aortic aneurysm or dissection - any prior-year use

A combined weighted comorbidity index was used to quantify each individual's burden of comorbidity.

Results

Current use of fluoroquinolones was found to be associated with increased risk for aortic aneurysm or dissection (rate ratio [RR], 2.43; 95%CI, 1.83-3.22). The increase in risk of aortic aneurysm or dissection remained after adjusting for individual confounders (RR, 2.28; 95% CI, 1.67-3.13), adjustment by propensity score (RR, 2.43; 95% CI, 1.83-3.22), and propensity score matching (RR, 1.75; 95%CI, 1.11-2.74). Past use of fluoroquinolone was also associated with a higher risk, although this risk was attenuated (RR, 1.48; 95%CI, 1.18-1.86). Use of fluoroquinolones was associated with an approximately 2-fold increase in risk of aortic aneurysm and dissection within 60 days of exposure.

Sensitivity analysis focusing on aortic aneurysm and dissection requiring surgery did not show any statistically significant differences between groups. The risk increase of aortic aneurysm or dissection in any prior year use of fluoroquinolone was more substantial in patients older than 70 years (RR, 1.72; 95% CI, 1.37-2.16) than in patients 70 years or younger (RR, 1.46; 95% CI, 0.98-2.18) and more substantial in female patients. Patients with aortic aneurysm or dissection were found to have a higher burden of cardiovascular diseases.

The relationship between duration of fluoroquinolone therapy and risk of aortic aneurysm and dissection is shown in Table 6. As the duration of fluoroquinolone therapy increased from 3 to14 days, there was an increasing risk of aortic aneurysm or dissection.

Table 6.

Table 4. Risk of Aortic Aneurysm or Aortic Dissection Associated With Increasing Duration of Fluoroquinolone Use

Duration of Fluoroquinolone Use, d	Case/Person-years, No. (Incidence Rate, %)	Propensity Score–Adjusted Rate Ratio (95% CI)
<3 [Reference]	1432/147 495 (0.97)	1 [Reference]
3-14	33/1271 (2.60)	1.60 (1.10-2.52)[a]
>14	12/411 (2.92)	1.81 (0.91-3.17)

[a] $P < .05$.

Comment: The risk increased with longer duration of therapy in this study but the difference is not statistically significant when the durations is more than 14 days. Note that the number of cases are very small.

3.1.4 Daneman N, Lu H, Redelmeier DA, 2015, Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study (23)

This population-based longitudinal cohort study was set in Ontario, Canada. The primary outcome measures were severe collagen associated adverse events defined as tendon ruptures, retinal detachments and aortic aneurysms diagnosed in hospital and emergency departments. For aortic aneurysm diagnoses, also the proportion that were complicated by aortic rupture or dissection and the proportion that were labelled as the primary most responsible diagnoses were measured.

Methods
Ontario adults turning 65 years, during a 15-year period between 1 April 1997 and 31 March 2012 were included. Individuals were accrued on their 65th birthday and followed until death, an outcome event, or the end of the study period (31 March 2014), thereby providing a minimum of 2 years and a maximum of 17 years follow-up.

Fluoroquinolone prescriptions were measured in the Ontario Drug Benefits (ODB) database which records medicines prescribed to older Ontario patients. Individuals over the age of 65 get free medication with minimal co-payment in Ontario. Available fluoroquinolones (ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin, and ofloxacin) were quantified based on the number of days of treatment supplied, and patients were considered at risk for up to 30 days following a treatment course.

Each outcome was examined in a separate multivariate Cox proportional hazards model to allow coefficients to differ for the primary predictor (fluoroquinolone exposure) as well as for other risk factors. Patients were censored on the primary outcome event, death or the end of the study. Models were examined with and without adjustment for demographic, healthcare utilisation and comorbidity variables. Sensitivity analyses were performed. To test the specificity of the findings, absence of an association between amoxicillin prescriptions and the same adverse events were tested for.

Results

A total of 1 744 360 patients were identified. More than one-third (38%) received at least one fluoroquinolone prescription during follow-up, with a mean of 1.3±3.6 prescriptions per patient, amounting to a total of 2 260 994 fluoroquinolone prescriptions.

The most common fluoroquinolone was ciprofloxacin (50%), followed by norfloxacin (18%) and moxifloxacin (16%). The most common prescription duration was 7 days (35%), but nearly half the prescriptions exceeded 7 days (1 056 492, 47%). In total, 22 380 515 total patient-days of fluoroquinolone treatment were observed.

The patients experienced 37 338 (2.1%) tendon ruptures, 3246 (0.2%) retinal detachments, and 18 391 (1.1%) aortic aneurysms. Current fluoroquinolone use was associated with an increased hazard of tendon rupture (HR 3.13, 95% CI 2.98 to 3.28; adjusted HR 2.40, 95% CI 2.24 to 2.57) and an increased hazard of aortic aneurysms (HR 2.72, 95% CI 2.53 to 2.93; adjusted HR2.24, 95% CI 2.02 to 2.49) that were substantially greater in magnitude than the association of these outcomes with amoxicillin, see table 7 below:

Table 7.

Table 2   Current fluoroquinolone use* and the hazard of collagen-associated adverse events

Antibiotic exposure outcome event	Unadjusted HR	95% CI	Adjusted† HR	95% CI
Fluoroquinolones				
Tendon rupture	3.13	2.98 to 3.28	2.40	2.24 to 2.57
Retinal detachment	1.28	0.99 to 1.65	1.47	1.08 to 2.00
Aortic aneurysm	2.72	2.53 to 2.93	2.24	2.02 to 2.49
Amoxicillin (negative tracer)				
Tendon rupture	1.56	1.46 to 1.66	1.41	1.29 to 1.54
Retinal detachment	1.44	1.14 to 1.81	1.47	1.08 to 2.00
Aortic aneurysm	1.74	1.59 to 1.90	1.50	1.32 to 1.70

*Patients considered exposed during fluoroquinolone course and for 30 days following treatment.
†Adjusted for baseline characteristics including sex, income quintile, prior hospital admissions, prior physician visits, diabetes mellitus, hypertension, atherosclerosis, chronic kidney disease, chronic obstructive pulmonary disease, hypothyroidism, depression, inflammatory bowel disease, malignancy, liver disease, prior pneumonia, prior urinary tract infection.

The magnitude of the association of fluoroquinolones and aortic aneurysm events was stronger than the association observed with other aneurysm risk factors such as hypertension and atherosclerosis. The subsequent risk of rupture or dissection was 155/762 (20.3%) among aneurysms diagnosed during fluoroquinolone prescriptions. The association of fluoroquinolones with subsequent aortic aneurysms was robust across multiple pre-specified utilisation and patient comorbidity. The median time from fluoroquinolone initiation to aortic aneurysm was 20 days.

Comments: The prescribing of fluoroquinolones to elderly patients is remarkably high in this study. Both Lee, Daneman and Pasternak demonstrated about a 2-fold increased risk of AA or AD in patients exposed to fluoroquinolones compared to patients not exposed to fluoroquinolones or exposed to amoxicillin. Note that the patients in the study by Daneman and Pasternak were elderly. In the studies by Pasternak and Lee, the hazard period was 60 days, and there was no increased risk of AA/AD when the hazard period was extended beyond 60 days.

3.1.5   Singh S, Nautiyal A, 2017, Aortic Dissection and Aortic Aneurysms Associated with Fluoroquinolones: A Systemic Review and Meta-Analysis (19)

Methods

The databases Medline, Embase, and Scopus were searched from inception to February 15, 2017. Controlled studies were selected for inclusion if they reported data on aortic dissection and aortic aneurysm associated with fluoroquinolones exposure versus no exposure.

The quality of studies were assessed by the Newcastle–Ottawa Scale for observational studies and the strength of evidence by using the Grading of Recommendations Assessment, Development, and Evaluation approach.

The odds ratios (ORs) from observational studies were pooled using the fixed-effect inverse variance method, and statistical heterogeneity was assessed using the I^2 statistic.

A total of 714 citations were reviewed and from these 2 observational studies were included in the meta-analysis. The included studies were:

- The case control study by Lee et al from 2015.
- The cohort study by Daneman

Both studies evaluated different types of fluoroquinolones. Exposure was defined using prescription databases in both studies. The case-control study defined 3 categories of exposure: 1) current exposure within 60 days of index date, 2) recent exposure within 60 days up to 365 days from the index date, and 3) any exposure up to 365 days from the index date. The cohort study defined current exposure as exposure up to 30 days after fluoroquinolone use.

Both studies used a combination of administrative diagnostic codes to identify aortic aneurysms and aortic dissection and a wide variety of variables to adjust for potential confounders, including smoking, hypertension, diabetes, and cardiovascular risk factors. Propensity score methods was used to adjust for confounding in both studies.

Results
Current use of fluoroquinolones was associated with a statistically significantly increased risk of aortic dissection (OR, 2.79; 95% confidence interval [CI], 2.31-3.37; I2 = 0%) and aortic aneurysm (OR, 2.25; 95% CI, 2.03-2.49; I2 = 0%) in a fixed-effects meta-analysis. The unadjusted OR estimates and sensitivity analysis using a random-effects model showed similar results. The strength of evidence was rated to be of moderate quality. The number needed to harm for aortic aneurysm for elderly patients aged more than 65 years who were current users of fluoroquinolones was estimated to be 618 (95% CI, 518-749). Differences among past users or any users were smaller.

The authors suggest an increased relative risk, although the absolute risk is modest and evidence is of moderate quality. Clinicians should consider the risk, especially when treating patients with additional risk factors.

3.1.6   Noman AT, Qazi AH, Alqasrawi M et al, 2018, Fluoroquinolones and the risk of aortopathy: A systematic review and meta-analysis (24)

In this meta-analysis 3 publications were included out of 610 retrieved in the initial search: the same two as in the analysis by Singh et al and also the study by Pasternak et al.

Methods
The Newcastle–Ottawa quality assessment scale (NOS) was used to evaluate the quality of observational studies. NOS scale rates observational studies based on 3 parameters: selection, comparability between the exposed and unexposed groups, and exposure/outcome assessment.
A meta-analytical approach using inverse variance method was used to pool studies' adjusted odds ratio or hazards ratio into a random effects model. Odds ratios or hazards ratios from propensity score matching were used whenever available or from adjusted multivariate analysis when propensity score matching was not available.

The primary outcome of interest was occurrence of aortic aneurysm or dissection with current fluoroquinolone use (defined as within 60 days from occurrence of the outcome) in comparison to control. Incidence of aortic aneurysm or aortic dissection were also analysed separately and compared to a control group.

Results

All three included studies scored high on the NOS. Current use of fluoroquinolones was associated with significantly elevated risk of developing aortic aneurysm and/or dissection in comparison to controls, (OR = 2.04; 95% CI [1.67, 2.48]). There was only a mild degree of between study heterogeneity, I^2 = 33%. See figure 10:

Figure 10.
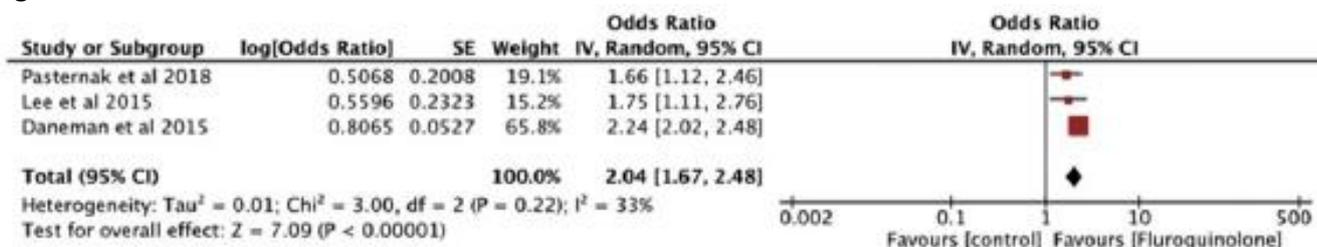
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Pasternak et al 2018	0.5068	0.2008	19.1%	1.66 [1.12, 2.46]
Lee et al 2015	0.5596	0.2323	15.2%	1.75 [1.11, 2.76]
Daneman et al 2015	0.8065	0.0527	65.8%	2.24 [2.02, 2.48]
Total (95% CI)			100.0%	2.04 [1.67, 2.48]

Heterogeneity: Tau² = 0.01; Chi² = 3.00, df = 2 (P = 0.22); I² = 33%
Test for overall effect: Z = 7.09 (P < 0.00001)

Fluoroquinolone use was associated with significantly elevated risk of developing aortic aneurysm (OR=2.23; 95% CI [2.03, 2.46]; I2=0%) as well as aortic dissection (OR = 2.25; 95% CI [1.42, 3.56]; I2 = 65%) in comparison to control group, when these endpoints were analysed separately.

The authors estimate the number needed to harm (cause an episode of aortic aneurysm or dissection) to be 1376 treatment courses of fluoroquinolones, which becomes alarming given the high use of fluoroquinolones and the devastating effects of aortic aneurysm and/or dissection. The authors also note a study which estimated that 1 out of 3 fluoroquinolones prescriptions to hospitalised patients were unnecessary (25).

Comment: The meta-analysis by Norman et al also included the study with active control (Pasternak).

3.1.7   Frankel WC, Trautner BW, Spiegelman A et al, 2019, Patients at risk for aortic rupture often exposed to fluoroquinolones during hospitalisation (26)

The aim of this retrospective cohort study was to determine the prevalence of systemic fluoroquinolone exposure and predictors of fluoroquinolone use in patients with aortic aneurysm or dissection (AAD) or Marfan syndrome. These groups of patients have been described as having an increased risk of developing aortic rupture.

Methods

Data were obtained from the advisory board billing and administrative database, which contained information on 22 million adult hospitalizations in the United States for the study period (2009 to 2015). International Classification of Diseases (9/10) and Current Procedural Terminology codes were used to identify patients who had AAD or Marfan syndrome or underwent aortic repair.

Results

A total of 136,789 admissions for AAD were identified, which involved 99,818 unique patients, 67% of them were men. Of those, 20% received fluoroquinolone during a hospital admission. Of the 7,045 patients with dissection, 18% were exposed to fluoroquinolone. Of the 27,876 AAD patients who underwent aortic repair, 19% received fluoroquinolone during a hospitalization before the repair. Exposure to fluoroquinolones was lower during or after the repair. In the AAD patients, having a diagnosis of pneumonia or urinary tract infection increased the likelihood of receiving fluoroquinolone during admission by 46% and 40%, respectively (P<0.001).

Additionally, 2,871 admissions for Marfan syndrome were identified, which involved 1,872 patients. Fourteen percent of these patients received fluoroquinolone during an admission. Pneumonia and urinary tract infections increased the risk of fluoroquinolone exposure.

The authors conclude that a large number of patients with AAD, including those with unrepaired lesions, are receiving fluoroquinolones and if the suspected deleterious effect of fluoroquinolones on aortic integrity is substantiated, reducing use in these patients need to be addressed.

> *Comments:* Dispensing data to patients >65 in NZ is provided in this report (section 2.1.8). If these patients also belong to other risk groups is unknown.

3.1.8 Meng L, Huang J, Jia Y, 2019, Assessing fluoroquinolone+associated aortic aneurysm and dissection data mining of the public version of the FDA Adverse Event Reporting System (18)

This is an article from China, analysing public data from the FDA Adverse Event Reporting System (FAERS). The aim was to assess aortic aneurysms or dissections induced by fluoroquinolones, the relationship between administration routes and the specified adverse events, and to determine the rank-order of the association.

Methods

Ciprofloxacin, levofloxacin, and moxifloxacin were selected as study drugs, and cefuroxime was chosen as the negative exposure control. Data were retrieved from the FAERS database covering the period from January 1, 2004 to December 31, 2016 and disproportionality analysis was used. This means that the proportion of specific adverse events occuring for a specific study drug is compared to the proportion for all other drugs. When a specific drug is more likely to induce a specific adverse event than all other drugs, it will typically receive a higher score due to a higher disproportionality.

Frequentist and Bayesian methods were used to calculate disproportionality by using reporting odds ratio (ROR), proportional reporting ratio (PRR), information component, IC (a logarithmic RRR metric that is implemented in a Bayesian framework), and the empirical Bayes geometric mean, EBGM (the relative reporting ratio (RRR), when implemented within an empirical Bayesian framework). These algorithms extract decision rules for signal detection and/or calculating scores to measure associations between drugs and adverse events from case reports.

Indication of a drug-associated adverse event being a safety signal was when at least one of the four indices met the aforementioned criteria:

- With ROR signal detection: the lower bound of the 95% two-sided confidence interval (CI) exceeded 1.0.
- With PRR signal detection: the count of case is ≥ 3.0 and the PRR is ≥ 2.0 with an associated χ^2 value of ≥ 4.0.
- With IC signal detection: the IC025 metric, which is a lower bound of the 95% two-sided CI of IC is exceeding 0.
- With EBGM signal detection: the EB05, which is a lower one-sided 95% confidence bound of the EBGM, is ≥ 2.0.

Results

During the study period, the FAERS database received a total of 7,153,801 adverse event reports (ADR): 2,713 for aortic aneurysms and 1,008 for aortic dissections. Event numbers are shown in table 8. More cases were reported for older patients.

Table 8. Signal detections for ciprofloxacin-, levofloxacin-, and moxifloxacin-associated aortic aneurysm and dissection.

	Ciprofloxacin		Levofloxacin		Moxifloxacin	
	Aortic aneurysm	Aortic dissection	Aortic aneurysm	Aortic dissection	Aortic aneurysm	Aortic dissection
Number of events of aortic aneurysm or dissection	31	7	67	17	27	4

The signal scores suggested that all three fluoroquinolones were associated with aortic aneurysm, and levofloxacin is associated with aortic dissection, whereas no significant signals are detected for cefuroxime, the negative control, see table 9:

Table 9.

Table 3. Signal detections for ciprofloxacin-, levofloxacin-, and moxifloxacin-associated aortic aneurysm and dissection (cefuroxime used as a negative exposure control)

		N	ROR (95% CI)	PRR (χ^2)	IC (95% CI)	EBGM (95% one-sided CI)
Aortic aneurysm	Ciprofloxacin	31	2.31(1.62,3.29)†	2.31(22.69)†	1.20(0.70,1.70)†	2.29(1.71)
	Levofloxacin	70	5.03(3.97,6.38)†	5.02(219.90)†	1.68(1.96,2.63)	4.92(4.05)†
	Moxifloxacin	27	4.18(2.86,6.11)†	4.18(64.63)†	2.05(1.52,2.59)†	4.15(3.04)†
	Cefuroxime	3	1.68(0.54,5.23)	1.68(0.83)	0.75(-0.66,2.17)	1.68(0.74)
Aortic dissection	Ciprofloxacin	7	1.40(0.66,2.94)	1.40(0.78)	0.48(-0.52,1.02)	1.39(0.78)
	Levofloxacin	17	3.26(2.02,5.26)†	3.25(26.10)†	1.69(1.02,2.35)†	3.22(2.18)†
	Moxifloxacin	4	1.66(0.62,4.42)	1.66(1.03)	0.73(-0.54,1.99)	1.65(0.79)
	Cefuroxime	1	1.51(0.21,10.72)	1.50(0.17)	0.59(-1.41,2.59)	1.50(0.47)

N: number of adverse event reports.
PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.
CI: confidence interval; two-sided for ROR and IC, and one-sided for EBGM.
†: signal detected, see ''Methods'' for the criteria of detection.

The results showed that Levofloxacin was associated with a higher risk than ciprofloxacin and moxifloxacin. Oral administration of fluoroquinolones was more likely to produce these adverse events than intravenous administration.

Comment: Note that the study by Meng is a kind of study that detects signals but cannot confirm associations like an observational study can. In addition, those kind of studies are subject to reporting bias.

3.2   Regulatory action

3.2.1   Risk of aortic aneurysm and dissection

3.2.1.1 EMA – PRAC

EMA published a recommendation in 2018 regarding systemic and inhaled fluoroquinolones (27, 28). MAHs are to submit a variation to amend the product information with the following text:

4.4. Special warnings and precautions for use

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or

conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

The MAHs are also required to amend the package leaflet. A Direct Healthcare Professional Communication (DHPC) will be circulated, stating:

- Systemic and inhaled fluoroquinolones may increase the risk of aortic aneurysm and dissection, particularly in older people.

- In patients at risk for aortic aneurysm and dissection, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.

- Conditions predisposing to aortic aneurysm and dissection include a family history of aneurysm disease, pre-existing aortic aneurysm or aortic dissection, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, and atherosclerosis.

- Patients should be advised about risk of aortic aneurysm and dissection and told to seek immediate medical attention in the emergency department in case of sudden severe abdominal, chest or back pain.

Bayer has accepted the revision of the EU SPC as local deviation.

3.2.1.2 FDA

FDA state that they have received over 1700 reports of aortic aneurysm or dissection with fluoroquinolone use from December 16, 2015 through April 30, 2018; however, the vast majority are litigation reports with limited clinical information. Of the postmarketing reports that had sufficient clinical information for assessment, all described at least one well-defined risk factor (i.e., advanced age, smoking, hypertension, male gender, atherosclerosis) associated with the development of aortic aneurysms or dissection.

In December 2018, a warning and a safety communication was issued (29). FDAs review, based on reported cases and the published observational studies described in this report, concluded that there is consistent evidence of an association between fluoroquinolone use (oral or parenteral) and aortic aneurysm or dissection.

Fluoroquinolones should not be used in patients at increased risk unless there are no other treatment options available. People at increased risk include those with a history of blockages or aneurysms (abnormal bulges) of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes, and the elderly. FDA are requiring that a new warning about this risk be added to the prescribing information and patient Medication Guide for all fluoroquinolones. The procedure is ongoing. Note that norfloxacin is no longer available in the US.

3.2.2 Risk of disabling and persistent musculoskeletal and nervous system adverse reactions

3.2.2.1 Medsafe

At the December 2017 meeting, the MARC discussed this safety concern. FDA, Health Canada and TGA had recommended to update product information and EMA was reviewing the issue.

The Committee noted the available data on the potential risk of disabling and persistent musculoskeletal and nervous system adverse reactions from the use of fluoroquinolones is limited to case reports and case series. The Committee recommended information on these risks should be included in fluoroquinolone data sheets and consumer medicine information.

Medsafe asked the MAHs to update section 4.4 of their data sheets with the following text:

4.4 Special warnings and precautions for use

Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.

To date, Mylan and Bayer have updated their data sheets for ciprofloxacin, but the CMI does not contain information about that these effects can be persistent. Rex, Pharmacy Retailing and AFT have not updated their product information.

TEVA has updated the data sheet for norfloxacin but not the CMI. Bayer has updated the data sheet for moxifloxacin but not the CMI.

3.2.2.2 Results of the EMA review

The review by EMA is now completed with the result to ask for updates of the prescribing information for healthcare professionals and information for patients. An unusual ingredient in the review was a public hearing that was held in June 2018 to hear the views of patients and the general public on the persistence of side effects reported with fluoroquinolones (30, 31).

Sixty-nine participants attended in person at EMA offices in London (or called in by telephone), including 40 patients and patient representatives, 14 healthcare professionals and academics, 13 representatives from pharmaceutical industry as well as members of the media. Many other members of the public who could not attend sent submissions in writing. Many followed the meeting on the web.

Patients described life-changing symptoms following treatment with quinolone and fluoroquinolone antibiotics, including pain and disability lasting several years, with some patients only experiencing limited improvement over time. Furthermore, some patients could no longer work or engage in exercise and active pursuits or even carry out daily tasks such as tying a shoe lace or buttoning a shirt; some were in constant pain, with symptoms affecting a wide range of muscles and tendons.

The tendon problems generally affected multiple tendons, in contrast to many other tendon disorders which usually affect one. Other symptoms include mood disturbances and other mental health effects as well as effects on the heart. These side effects were reported by patients who took medicines by mouth or injection and medicines given as ear and eye drops were also considered to cause them. In many cases, quinolones and fluoroquinolones had been prescribed for minor infections or were used to prevent infection.

The hearing resulted in a list of proposals, see Figure 10. The views were incorporated in the review.

Figure 11.

Proposals
• Restrict quinolone and fluoroquinolone use to situations where there are no alternatives.
• Improve education for healthcare professionals (including during medical training).
• Improve management of patients with side effects (taking account of wide-ranging symptoms).
• Improve communication on quinolone and fluoroquinolone toxicity, including possible risk factors, and add more information in the product information, including the package leaflet.
• Encourage research on how the medicines cause side effects, including genetic research.
• Consider how certain foods affect patients' symptoms, particularly meat treated with quinolones and fluoroquinolones.

3.2.3 Restrictions to indications for use

3.2.3.1 FDA

In 2016, the US Food and Drug Administration (FDA) stated that the serious adverse effects associated with fluoroquinolones generally outweigh the benefits for patients with:

- acute bacterial sinusitis
- acute bacterial exacerbation of chronic bronchitis
- uncomplicated urinary tract infections who have other treatment options.

For patients with these infections, fluoroquinolones should be reserved for those who have no alternative treatment options (32, 33). In the product information this is reflected in the indication section, as a note that for certain indications, fluoroquinolones should only be used if there is no other treatment option.

3.2.3.2 EMA

Following the review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics given by mouth, injection or inhalation and the public hearing, EMA decided that the marketing authorisation of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended (34).

In addition, the CHMP confirmed that the use of the remaining fluoroquinolone antibiotics should be restricted. In addition, the prescribing information for healthcare professionals and information for patients will describe the disabling and potentially permanent side effects and advice patients to stop treatment with a fluoroquinolone antibiotic at the first sign of a side effect involving muscles, tendons or joints and the nervous system.

Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

They also state that: "Importantly, fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided".

3.2.3.3 Medsafe

The MARC Committee discussed this issue on the December 2017 meeting. From the minutes: "The Committee discussed antibiotic stewardship by prescribers to reduce antimicrobial resistance. The Committee noted the 2017 edition of the antibiotic guide produced by the Best Practice Advocacy Centre (BPAC) recommends fluoroquinolones are used second-line for urinary tract infections and are not listed as first choice or alternatives for respiratory indications. The Committee also discussed the use of fluoroquinolones in secondary care. The Committee considered this is a broader public health issue and there are awareness campaigns to ensure that antibiotics are prescribed and used appropriately. Indications as listed in fluoroquinolone data sheets are sufficient and do not require further restriction at this time".

Comments: In NZ, moxifloxacin has the indication acute sinusitis and acute exacerbations of chronic bronchitis. Also, the therapeutic indications of moxifloxacin do not match with the funding in PHARMACs Pharmaceutical Schedule. Norfloxacin has the indication complicated and uncomplicated acute urinary tract infections. Other indications include the word "uncomplicated" for all three fluoroquinolones on the market.

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3.4   CARM data

A search covering all spontaneous reports received by the Centre for Adverse Reactions Monitoring [CARM] up to 31 March 2019 did not reveal any cases aortic aneurysm or dissection with any fluoroquinolone on the CARM database.

4   DISCUSSION AND CONCLUSIONS

There are three fluoroquinolone antibiotics available in NZ. They are useful for treatment of several bacterial infections, including life-threatening ones, even if growing resistance problems limit their use.

Data from recent observational studies have indicated an about 2-fold increased risk of aortic aneurysm and dissection in patients taking systemic fluoroquinolones compared with patients taking no antibiotics or other antibiotics (amoxicillin).

Aortic aneurysm or dissection are rarely occurring, very severe conditions with a high rate of mortality. The aortic aneurysm slowly progresses during which time the bulge in the weakened area of the aorta balloons, and symptoms often do not show until it bursts. Onset of aortic dissection is often sudden with severe chest or back pain when the large blood vessel tears and blood comes through the wall.

The annual background risk of aortic aneurysm or dissection is hard to predict but numbers stated in the literature has been between 3 and 20 per 100,000 population, with much higher numbers (100-300 per 100,000) among the oldest. Other risk factors are for example a family history of aneurysm disease, pre-existing aortic aneurysm and/or aortic dissection and atherosclerosis.

The study by Pasternak reported a rate of aortic aneurysm or dissection of 1.2 cases per 1000 person-years among fluoroquinolone treatment episodes versus 0.7 cases per 1000 person-years among amoxicillin treatment episodes, corresponding to an estimated absolute difference of 82 cases of aortic aneurysm or dissection by 60 days per 1 million treatment episodes.

A rate of aortic aneurysms diagnosed in hospital and emergency departments as 3.5 per 1000 person-years for patients currently using fluoroquinolones versus 1.3 per 1000 person-years for patients not using fluoroquinolones was reported in study by Daneman of patients aged 65 years and older in Canada.

The data from the studies do not allow for differentiation between risks at different durations of treatment. In the Pasternak study, 41% of cases of aortic rupture occurred in the first 10 days of quinolone treatment and there was was no increased risk associated with fluoroquinolone exposure in the period of 61-120 days from start of treatment. The Daneman study showed a median of 20 days of therapy at time of rupture. In the study by Lee 2018, an increased risk of AA/AD was observed if the patient had more than 14 days exposure to fluoroquinolones.

The observational nature of the studies leave room for potential confounders and there are uncertainties regarding unknown factors like co-morbidities, scanning frequency or co-medication, or if selected comparative treatments were the right ones.

The results of the studies suggest that there is an association. And given these results, it cannot be ruled out that an association may be present. The size of the risk is small but still substantial given the use of

fluoroquinolones, especially if patients also have other risk factors. Usage data from NZ shows that ciprofloxacin is decreasing but still high, while moxifloxacin use is increasing, also for patients over 65 years of age. Note that these data do not cover hospital use.

There is a suggested mechanism for how fluoroquinolones may affect the aorta by direct toxicity to type I collagen synthesis collagen degradation. Type I and type III collagen comprise the majority of collagen (80–90%) in the aorta and also in the Achilles tendon, thereby suggesting that fluoroquinolones could destroy collagen along the aortic wall leading to aortic aneurysm or dissection as they do on tendons.
One question is how quickly fluoroquinolones would affect the collagen. For example, in the study by Pasternak, the reaction came early after start of fluoroquinolone treatment. ████████████████████
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The Committee is asked to advise whether a warning is warranted to alert health care professionals and patients regarding this adverse reaction, addressing that for patients at strong risk for aortic aneurysm and dissection, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.

Following the review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics, use of fluoroquinolones has been restricted in some countries to not be first line treatment in mild to moderate infections. This was discussed at the December 2017 MARC meeting and the Committee concluded that no action was necessary as NZ guidelines emphasize the correct use.

However, moxifloxacin has the indication acute sinusitis and acute exacerbations of chronic bronchitis. Also, the therapeutic indications of moxifloxacin do not match with the funding in PHARMACs Pharmaceutical Schedule. Norfloxacin has the indication complicated and uncomplicated acute urinary tract infections. Other indications include the word "uncomplicated" for all three fluoroquinolones on the market. Therefore the Committee is asked again whether indications for fluoroquinolones should be restricted.

5   ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets should be updated regarding the risk of aortic aneurysm and dissection
- The indications for fluoroquinolones should be restricted
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6   ANNEXES

Annexe 1: Report from Bayer.
Annexe 2: Pasternak et al 2018.
Annexe 3: Lee et al 2018.
Annexe 4: Lee et al 2015.
Annexe 5: Daneman et al 2015.

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