

# What Fluoroquinolones Have the Highest Risk of Aortic Aneurysm? A Case/Non-case Study in VigiBase®

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**KEY WORDS:** fluoroquinolones; levofloxacin; aortic aneurysms; aortic dissection.

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## INTRODUCTION

Fluoroquinolones have a broad antimicrobial activity and are one of the most commonly prescribed groups of antibiotics. They are widely used for the treatment of many infections affecting among others the urinary, gastro-intestinal, abdominal, or respiratory tract. Recently, fluoroquinolones were associated with an increased risk of aortic aneurysms and dissections,<sup>1–3</sup> with an excess risk of 0.5 cases per 1000 person-years for fluoroquinolone users versus amoxicillin users.<sup>3</sup> However, these studies were underpowered to distinguish between different fluoroquinolones. Therefore, we assessed the specific risk of individual fluoroquinolones for aortic aneurysms and dissections, using the case/non-case design, a method validated to detect very rare events.<sup>4</sup>

## METHODS

The study was conducted using VigiBase®, the World Health Organization Global Individual Case Safety Reports (ICSRs) database which includes more than 16 million reports forwarded to the WHO Uppsala Monitoring Center by national pharmacovigilance systems from over 130 countries around the world since 1967. Only ICSRs registered between 1972 and 2017, with known age and sex and concerning patients ≥ 50 years, were included. Cases were ICSRs containing the term “aortic aneurysms and dissections” according to the MedDRA dictionary. Reports registered under the term “aortic aneurysm syphilitic” were excluded. Non-cases were all other reports during the same period. Exposure to fluoroquinolones was compared to amoxicillin exposure. We also assessed the risk of individual fluoroquinolones, thereby excluding ICSRs

with more than one fluoroquinolone. The case/non-case method allows the calculation of reporting odds ratios (ROR) with their 95% confidence intervals (CI) of the exposure odds among reported cases of aortic aneurysms and dissections to the exposure odds among reported non-cases.<sup>4</sup> ROR adjusted for age, sex, year of report, continent of report, notifier type, and number of drugs prescribed were analyzed by multivariable logistic regression. Similar investigations were made with the ICSRs of “tendon injury, pain, rupture, and tendinitis,” a known adverse drug reaction of fluoroquinolones. Institutional review board approval was not required because VigiBase® is an unlikable anonymized database open to pharmacovigilance centers.

## RESULTS

Among the 6,383,318 ICSRs registered in VigiBase® between 1972 and 2017, 172,588 were reported with fluoroquinolones and 40,658 with amoxicillin. We found 113 aortic aneurysms or dissections with fluoroquinolones (including 12 with more than 1 fluoroquinolone) and 8 with amoxicillin. Fluoroquinolone exposure was associated with a higher risk of reporting aneurysms/dissections compared to amoxicillin exposure (ROR 2.13, 95% CI 1.03–4.37). Compared with use of other fluoroquinolones, an elevated ROR was observed only with levofloxacin (ROR 2.78, 95% CI 1.83–4.23) (Table 1). For tendon disorders, an increase in the ROR was found for fluoroquinolones versus amoxicillin (ROR 122.48, 95% CI 80.60–186.14). When each fluoroquinolone was compared to all other fluoroquinolones, only two fluoroquinolones were associated with a significantly increased ROR for tendon disorders: pefloxacin (ROR 3.12, 95% CI 2.67–3.66) and levofloxacin (ROR 3.55, 95% CI 3.38–3.72).

## DISCUSSION

The present study corroborated previous data suggesting an increased risk of aortic aneurysms and dissections

**Table 1 Crude and Adjusted Reporting Odds Ratios for the Association Between Aortic Aneurysms or Dissections and the Use of Individual Fluoroquinolones in Vigibase® (Comparisons Were Made Between Each Fluoroquinolone and All Other Ones Excluding Individual Case Safety Reports with More Than One Fluoroquinolone. No Case of Aneurysms or Dissections Was Reported with Enoxacin, Fleroxacin, Gemifloxacin, Grepafloxacin, Lomefloxacin, Norfloxacin, Pazufloxacin, Pefloxacin, Prulifloxacin, Rufloxacin, Sparfloxacin, Temafloxacin, Trovafloxacin)**

	Cases <sup>b</sup>	Non-cases	Crude ROR	Adjusted ROR <sup>c</sup> (95% CI)
Levofloxacin	67	63,932	3.25	2.78 (1.83 4.23)
Ciprofloxacin	18	57,538	0.42	0.33 (0.20 0.55)
Moxifloxacin	10	16,687	1.01	0.86 (0.45 1.66)
Ofloxacin	3	12,330	0.39	1.29 (0.40 4.15)
Gatifloxacin	2	3008	<sup>d</sup>	<sup>d</sup>
Tosufloxacin	1	300	<sup>d</sup>	<sup>d</sup>

ROR, reporting odds ratio; CI, confidence interval; 95% CI, 95% confidence interval

<sup>b</sup>Cases of aortic aneurysms and dissections

<sup>c</sup>Reporting odds ratio was adjusted on age, sex, notifier (physician vs. others), continent (Americas, Asia, and others), year of notification, number of other drugs prescribed

<sup>d</sup>Reporting odds ratio was only calculated when cases  $\geq 3$

associated with fluoroquinolones. Importantly, it also suggested that among fluoroquinolones, only levofloxacin was associated with an increased risk of this adverse drug reaction. Our observation that levofloxacin was also associated with an increased risk of tendon disorders could indicate a common pharmacological mechanism for aortic aneurysm and tendon disorders, as well as a compound-specific risk. The study had some limitations. The main limitation is underreporting, as Vigibase® is based on spontaneous reports; however, it was previously shown that underreporting did not differ within the same therapeutic group of drugs.<sup>5</sup> Another concern is the possibility of confounding, including confounding by indication, comorbidity factors or unknown data associated with aneurysms. To attenuate this bias, we used an active comparator, i.e., amoxicillin, and we adjusted for several confounders including number of other drugs prescribed as a proxy of comorbid conditions. Owing to these limitations, the data indicate an increased risk of aortic aneurysms and dissections with levofloxacin compared to other fluoroquinolones, requiring further observational studies.

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### Compliance with Ethical Standards:

**Conflict of Interest:** The authors declare that they do not have a conflict of interest.

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