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Perspectives

# Association of fluoroquinolones use with the risk of aortic aneurysm or aortic dissection: Facts and myths

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Fluoroquinolones (FQs) are broad-spectrum antibiotics with excellent oral bioavailability, and can be used in many types of infections for both out-patient and hospitalized patients.[1—3] In Taiwan, the use of FQ is increasing notably with time.[4,5] However, safety issues regarding FQ-associated collagen disease events, such as tendon rupture and retinal detachment, remain a serious concern. Moreover, several observational studies conducted between 2015 and 2018 found that the use of FQ could be associated with an increased risk of aortic aneurysm (AA)/aortic detection (AD).[6—9] Two studies in Taiwan demonstrated that compared to non-users, oral FQ use was associated with a high risk of AA/AD.[7,8] Two other studies in Sweden and Canada found that a higher risk of AA/AD was observed in FQ users than in amoxicillin users.[6,9]

Toward the end of 2018, the US Food and Drug Administration (FDA) raised the cautionary level regarding the increased risk of ruptures or tears in the aortic blood vessel with FQ use and declared that FQ should not be used in patients at an increased risk, such as 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, unless there are no other treatment options available.[10] Furthermore, a recent study based on a US health insurance claims database found that FQ use was associated with an increased incidence of aneurysm formation (hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.17—1.24), compared with comparator antibiotics (amoxicillin-clavulanate, azithromycin, cephalexin, clindamycin, and trimethoprim/sulfamethoxazole).[11] Moreover, the association between FQ and the increased susceptibility to AD and aortic rupture through the suppression of lysyl oxidase expression and induction of matrix metalloproteinase expression has been demonstrated in an animal model[12] and that of the potential induction of human aortic myofibroblast-mediated extracellular matrix dysregulation in an *in vivo* study.[13]

However, after adjusting for infection indications and detection bias, several studies reported contradictory results.[14,15] Gopalakrishnan et al. used a US commercial claims database to conduct two cohort studies (pneumonia and urinary tract infection [UTI]) to assess potential confounding owing to indication bias or surveillance bias.[15] They found that the initiators of FQ had an increased rate of AA/AD compared with the initiators of azithromycin in the pneumonia cohort (HR, 2.57; 95% CI, 1.36—4.86), but no increased rate compared with the initiators of trimethoprim/sulfamethoxazole in the UTI cohort (HR, 0.99; 95% CI, 0.62—1.57).[15] To assess the possible confounding effect of co-existing infection, another nested case—control study in Taiwan used a nationwide population-based health insurance claims database to compare the risk of AA/AD associated with FQs vs other antibiotics with similar indication profiles among patients with the same types of infections.[14] Dong et al. found that any indicated infection was associated with an increase in AA/AD risk (adjusted odds ratio [OR], 1.73; 95% CI, 1.66—1.81), but not for FQs itself when compared with amoxicillin-clavulanate or ampicillin-sulbactam (OR, 1.01; 95% CI, 0.82—1.24) or with extended-spectrum cephalosporins (OR, 0.88; 95% CI, 0.70—1.11) among patients with indicated infections.[12] Two studies[14,15] suggested that the co-existing infection might play an important role in the development of AA/AD, and the possible mechanism could be septic emboli and bacterial seeding into the arterial wall, hemodynamic instability, and systemic inflammation-associated artery injury.[16,17] Thus, these two studies[14,15] emphasized the importance of the confounding effect of coexisting infections which were neglected in previous observational studies using real-world data.

In addition to the confounding effect of co-existing infection, several issues that should be considered regarding the risk of FQ-associated AA/AD risk have been discussed. First, most of the previous studies focused on the effect of short-term use of oral FQ; however, FQ could be used for weeks to months in several clinical entities. For patients with chronic bacterial prostatitis, FQs are considered as the first-line treatment owing to favorable prostate penetration, and a longer treatment duration, between 6 and 12 weeks, is often necessary to achieve pathogen eradication and prevent recurrence.[18] For nontuberculous mycobacterial pulmonary disease, FQ could be a part of antibiotic combination regimens and the recommended drugs may be administered for at least 12 months after culture conversion.[19] Another complicated infection requiring prolonged antibiotic treatment is multidrug-resistant tuberculosis (MDRTB). Levofloxacin or moxifloxacin should be included for the treatment of patients with MDRTB for 15—17 months after culture conversion for most patients.[20] If FQs are directly associated with the development of AA/AD, the dose—response relationship could be demonstrated and the risk of AA/AD is supposed to be the highest among patients receiving long-term use of FQs for chronic bacterial prostatitis, nontuberculous mycobacterial pulmonary disease, or MDRTB. However, no apparent dose—response association was observed in a study by Dong et al., in which the adjusted OR of AA/AD was 1.13, 0.74, and 1.04 for 3—7 days, 8—14 days, and >14 days of FQ use, respectively, compared to amoxicillin-clavulanate or ampicillin-sulbactam use.[14] Compared to extended-spectrum cephalosporins, the adjusted OR of AA/AD was 0.99, 0.65, and 0.91 for 3—7 days, 8—14 days, and >14 days of FQ, respectively. Further researches investigating the effect of long-term FQ use should be conducted to assess the dose—response relationship between FQ use and the risk of AA/AD. Second, the effect of causative microorganisms was not evaluated in all studies. However, the risk of AA/AD varies according to different pathogens. In addition to *Salmonella* species, which are notorious for the development of mycotic aneurysm, some pathogens such as *Staphylococcus, Enterococcus,* and *Streptococcus* species, could also cause infectious aortitis.[21] Thus, further studies are warranted to clarify the role of causative pathogens and to assess their associated confounding effect on this subject. Third, the confounding effect of surveillance or detection bias should be evaluated. In the study by Gopalakrishnan et al. the secondary analysis using amoxicillin as a comparator found that FQ use was associated with an increased rate of AA/AD compared with amoxicillin use (HR, 1.54; 95% CI, 1.33—1.79; incidence), but the higher risk of FQ use, compared to amoxicillin attenuated in those requiring baseline imaging in this cohort (HR, 1.13; 95% CI, 0.96—1.33).[15] Thus, surveillance bias was demonstrated to attenuate this kind of association. This kind of detection bias may explain why the significant association

between FQ and AA/AD was observed only in the pneumonia cohort but not in the UTI cohort in this study. More image studies were performed for patients with pneumonia than for those with UTI; therefore, a higher opportunity to detect asymptomatic AA could occur in the pneumonia cohort than in the UTI cohort.

Based on current evidence, clinicians should be alert to the risk of AA/AD while prescribing FQ. However, these complicated issues still have many uncertainties, such as dose—response relationships, the effect of causative pathogens, and the potential of surveillance bias. Further researches are warranted to clarify the role of FQ in the development of AA/AD.

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