apoptotic cells in the aortic walls of fluoroquinolone-treated Marfan mice compared with the vehicle-treated mice. This study is a logical extension of the authors' previous experimental work with mice with sporadic AAD, in which they demonstrated that fluoroquinolone treatment increased destruction of the aortic wall and increased the occurrence of rupture and premature death.⁷

There are some limitations to the study that the authors acknowledge. Only one fluoroquinolone was studied (ciprofloxacin), and dose-related effects were not investigated. Although the authors chose a clinically relevant dose, they administered it over the course of 28 days, which is longer than the typical clinical treatment course. The specific mouse fibrillin-1 mutation studied might not recapitulate the behavior of all fibrillin-1 mutations in human Marfan disease. Despite these limitations, this work links cause (fluoroquinolones) and effect (AAD) in a way that population-based studies have been unable to do. The

authors' conclusion that these drugs should be avoided in patients with Marfan syndrome is appropriate.

References

1. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen-associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5:e010077.
2. Lee CC, Lee MTG, Chen YS, Lee SH, Chen YS, Chen SC, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med*. 2015;175:1839-47.
3. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: Nationwide cohort study. *BMJ*. 2018;360:k678.
4. Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH Jr, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis*. 2015;60:1308-16.
5. Frankel WC, Trautner BW, Spiegelman A, Grigoryan L, LeMaire SA. Patients at risk for aortic rupture often exposed to fluoroquinolones during hospitalization. *Antimicrob Agents Chemother*. 2019;63:e0712-8.
6. LeMaire SA, Zhang L, Zhange NS, Luo W, Barrish JP, Zhang Q, et al. Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice. *J Thorac Cardiovasc Surg*. 2022;163:e215-26.
7. LeMaire SA, Zhang L, Luo W, Ren P, Azares AR, Wang Y, et al. Effect of ciprofloxacin on susceptibility to aortic dissection and rupture in mice. *JAMA Surg*. 2018;153:e181804.

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Commentary: Danger of fluoroquinolones in Marfan syndrome

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Fluoroquinolones are one of the most prescribed antibiotics and have been linked to the development of tendon rupture and nerve injury, earning them a black box warning from the US Food and Drug Administration.¹ Concerningly, previous clinical observational studies also have identified an association between fluoroquinolone use and the development of

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CENTRAL MESSAGE

New data using a murine model of Marfan syndrome reveal that ciprofloxacin can exacerbate the aortic phenotype.

aortic dissection and aortic aneurysm.^{2,3} LeMaire and colleagues⁴ previously demonstrated that ciprofloxacin increased the risk of aortic dissection and rupture in a mouse model of moderate, sporadic aortic aneurysm and dissection. In this issue of the *Journal*, LeMaire and colleagues⁵ extend

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their findings to a mouse model of Marfan syndrome using *Fbn1*^{C1041G/+} mice. Mice with Marfan syndrome given ciprofloxacin had increased aortic metalloproteinase expression and developed more rapid aortic enlargement as well as manifested a significantly increased predilection for aortic dissection and rupture. This study was conducted rigorously using group sizes that were adequately powered and using animals of both sexes. Interestingly, ciprofloxacin exacerbated the aortic phenotype in male mice whereas female mice appeared to be unaffected.

The aforementioned clinical observational studies as well as the carefully conducted experimental studies by LeMaire and colleagues underscore the risk of fluoroquinolones in patients who are at risk of developing aortic aneurysm, such as those with Marfan syndrome. Indeed, LeMaire and colleagues⁶ have recently reported that 14% of inpatients with Marfan syndrome were administered fluoroquinolones. Identifying a significantly greater rate of aortic complications in patients with aortic syndromes who have taken fluoroquinolones would strengthen the argument for the US Food and Drug Administration to render more specific warnings.

Interestingly, previous studies have identified a collagen defect associated with fluoroquinolone use.³ Collagen deficiency and defects caused by Ehlers–Danlos syndrome and osteogenesis imperfecta are known to cause arterial aneurysmal disease.^{7,8} Further, a recent study demonstrated that ciprofloxacin reduced type I collagen expression in human aortic fibroblasts in vitro.⁹ In their most recent study, LeMaire and colleagues did not identify an obvious deficiency fibrillar collagen quantity or quality in mice with

Marfan syndrome given ciprofloxacin, but perhaps more sensitive methods of detection are needed to identify changes or interrogating aortic tissue from animals earlier after ciprofloxacin treatment before end-stage aortic disease develops may be more revealing. Defining the mechanism by which fluoroquinolones predispose patients to developing aortic aneurysm and dissection may shed new insight into the pathogenesis of aortopathies as well as new targets to treat them.

References

1. Marchant J. When antibiotics turn toxic. *Nature*. 2018;555:431-3.
2. Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med*. 2015;175:1839-47.
3. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5:e010077.
4. LeMaire SA, Zhang L, Luo W, Ren P, Azares AR, Wang Y, et al. Effect of ciprofloxacin on susceptibility to aortic dissection and rupture in mice. *JAMA Surg*. 2018;153:e181804.
5. LeMaire SA, Zhang L, Zhange NS, Luo W, Barrish JP, Zhang Q, et al. Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice. *J Thorac Cardiovasc Surg*. 2022;163:e215-26.
6. Frankel WC, Trautner BW, Spiegelman A, Grigoryan L, LeMaire SA. Patients at risk for aortic rupture often exposed to fluoroquinolones during hospitalization. *Antimicrob Agents Chemother*. 2019;63:e01712-8.
7. Malfait F. Vascular aspects of the Ehlers-Danlos syndromes. *Matrix Biol*. 2018;71-72:380-95.
8. Primorac D, Anticevic D, Barisic I, Hudetz D, Ivkovic A. Osteogenesis imperfecta—multi-systemic and life-long disease that affects whole family. *Coll Antropol*. 2014;38:767-72.
9. Guzzardi DG, Teng G, Kang S, Geeraert PJ, Pattar SS, Svystonyuk DA, et al. Induction of human aortic myofibroblast-mediated extracellular matrix dysregulation: a potential mechanism of fluoroquinolone-associated aortopathy. *J Thorac Cardiovasc Surg*. 2019;157:109-19.e2.