aortopathy. This work offers a potentially causative explanation and encourages caution when using FQ antibiotics in patients with known connective tissue defects such as Marfan syndrome.

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Commentary: Fluoroquinolones and aortopathy—a basic (science) question?

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The normal human aorta is a sophisticated structure consisting of many cell types embedded in an extracellular matrix, which accounts for its ability to produce laminar flow at high pulsatile stress to offload the intracavitary pressure of the left ventricle and protect organ vascular beds from hypertension.¹ To achieve this, the aorta's cellular constituents and extracellular matrix (including elastin and collagen) are normally tightly regulated by a number of interacting pathways, including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases.²

Fluoroquinolones based on quinolone-4 act by inhibiting bacterial type II topoisomerases, gyrase, and topoisomerase IV and are used for a range of gram-negative and

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CENTRAL MESSAGE

Fluoroquinolones disturb the tightly regulated aortic ECM, resulting in dissection/rupture in a model of the Marfan syndrome; mechanistic studies are critical in addressing this urgent question.

gram-positive bacterial infections. They are widely used in real-world practice including in patients with aortic disease.³ Several observational studies have associated the use of fluoroquinolones with the development of aortic aneurysm and dissection,⁴⁻⁶ suggesting an alarming hazard ratio of 2.4 (95% confidence interval, 2.98-3.28) compared with amoxicillin, leading the Food and Drug Administration to advise against the use of fluoroquinolones in patients at risk of aortic disease in 2018. However, 2 studies recently published in *JAMA Internal Medicine*, a nested case-control study⁷ and a propensity-matched cohort study,⁸ suggest that the previous observational data on the association of fluoroquinolone use and aortopathy were critically flawed and raise a more interesting possibility—that surveillance bias and even bacterial

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infection in itself may be the driver of an apparent link between fluoroquinolone use and aortopathy.

Mechanistic data suggest that exposure of myofibroblasts cultured from human ascending aorta to fluoroquinolones alter the tissue inhibitors of metalloproteinases/MMP pathway and result in extracellular matrix breakdown.⁹ In this edition of *The Journal*, LeMaire and colleagues¹⁰ show an alarming impact of fluoroquinolones on the thoracic aorta of a mouse model of the Marfan syndrome based on *Fbn1* mutation. They show that exposure to a clinically relevant dose of fluoroquinolone results in significant aortic enlargement and dissection/rupture that is especially pronounced in *fbn1*-deficient mice. This appears to be due to an array of interacting pathways, including reduced LOX expression, increased MMP expression, and increased cell death. The result is elastic fiber fragmentation and an almost doubling of the rate of severe aneurysm and dissection in mice with Marfan syndrome. Interestingly, there was no impact on clinical aortic enlargement or dissection in normal mice, despite an effect on the histologic integrity of the aorta.

On the balance of the available data, the link between fluoroquinolone use and aortopathy remains unproven,¹¹ and previous studies indicating a link are likely due to the limitations of observational studies of rare events. Mechanistic, experimental data are fundamental in addressing this urgent question, and the authors are to be commended in addressing this critical knowledge gap. Further mechanistic data, perhaps using induced pluripotent stem cells or explanted Marfan aorta, will be essential in resolving this issue for the safety of our patients. A possible link between severe infection and aortopathy raises the possibility

of a hitherto-undescribed mechanism for aortic injury. This approach shows the supremacy of mechanistic studies in resolving clinically confusing situations in a way that “big data” cannot achieve. In the meantime, the risk and benefit of fluoroquinolone use will have to be assessed on an individual patient level.

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