See Article page e215.

Commentary: Fluoroquinolone antibiotics are antiaortic

David G. Guzzardi, PhD, Jameson Dundas, BHSc, and Paul W. M. Fedak, MD, PhD

Fluoroquinolone (FQ) antibiotics are used frequently for a variety of infections. Despite their widespread application, they are associated with aortic aneurysms, acute dissection, and rupture.¹ The Food and Drug Administration issued a “boxed warning” for the use of FQ for patients at risk of exacerbating pre-existing aortopathies, including Marfan syndrome.² We believe that this warning is not widely appreciated in the surgical community. There is growing clinical evidence for a strong association between FQ exposure and clinically significant aortic events. Yet, the mechanisms underlying this potentially dangerous relationship have not been fully elucidated. A cause-and-effect relationship is best revealed in the experimental laboratory and may be critical for pharmacovigilance.

In this edition of the *Journal*, LeMaire and colleagues³ explore the mechanisms of FQ-associated aortopathy. Leveraging an established murine model of Marfan syndrome, this study uncovers progressive aortic damage following ciprofloxacin exposure in these “at-risk” model animals. The histopathologic severity of the underlying aortopathy was worsened with FQ exposure. Histologic damage was supported mechanistically by an increased vascular expression of matrix proteases known to induce arterial dilatation. Metalloproteinase (MMP)-2, MMP-9, and cell death in the aortic wall were all significantly worsened with exposure to ciprofloxacin. Interestingly, the study also noted a decrease in lysyl oxidase expression in the

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CENTRAL MESSAGE

Fluoroquinolone antibiotic exposure exacerbates aortopathy in a mouse model of Marfan syndrome.

aortas of mice with Marfan syndrome that was worsened by FQ exposure. Lysyl oxidase may be important to the integrity of the vascular wall. These data build on the authors' previous work implicating FQ exposure in a murine model of sporadic aortic dissection under hypertensive challenge.⁴ Collectively, these findings further support aortic extracellular matrix (ECM) dysregulation and degradation as a cause for FQ-associated aortopathy.

We recently documented FQ-mediated ECM dysregulation in human aortic myofibroblasts.⁵ Similar to this study, we observed derangement of the MMP–tissue inhibitor of MMP axis, albeit as a decrease in tissue inhibitor of MMP expression. Although not reported in the present study, this lack of MMP inhibition may also contribute to FQ-associated aortopathy in Marfan syndrome. Interestingly, the authors also report sex differences in FQ-mediated aortopathy between male and female mice. Only male mice with Marfan syndrome had a statistically significant increase in rates of rupture and death. Although this study was not powered to interrogate sex differences, these data warrant further exploration. Whether these differences in male and female mice parallel those in human patients with Marfan syndrome is unclear, as is whether these ECM mechanisms are similarly found in human patients following FQ exposure. It is not clear if the deleterious effects of FQ exposure are found in other classes of antimicrobials, such as amoxicillin. Indeed, efforts to employ such a control group in clinical studies have shown no effects on aortopathy and suggest that the damage is specific to FQ use.¹

LeMaire and colleagues provide a valuable contribution to our mechanistic understanding of FQ-associated

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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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See Article page e215.

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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