JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 15, 2021

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Fluoroquinolones in Patients With Aortic Aneurysms or Dissections

Pouring Gasoline on a Fire*

Scott A. LeMaire, MD

Previous clinical studies regarding fluoroquinolones and aortic disease have focused entirely on the question of whether this class of antibiotics contributes to the development of aortic aneurysm and dissection in the general patient population. In 2015, 2 observational studies using large administrative datasets found that recent fluoroquinolone exposure was strongly associated with an increased risk of aortic aneurysm, dissection, and rupture (1,2). Although these findings raised serious concerns, the studies had many important limitations, leaving many—including the U.S. Food and Drug Administration (FDA) (3)—to seek additional evidence before calling for changes in clinical practice. In response, subsequent studies have used refined approaches to study design and analysis to mitigate various limitations. Although some of those studies (4-7) have corroborated the association between fluoroquinolone exposure and aortic disease, 2 recent papers (8,9) have cast doubt on the association, highlighting potential problems with bias and confounding factors. Taken together, the issue of whether fluoroquinolones cause aortic aneurysm or dissection in patients without pre-existing aortopathy remains unresolved (10).

Although it is unclear whether fluoroquinolones trigger de novo aortic disease, the potential for this association has raised several other pressing clinical questions. Of immediate concern is the question of whether fluoroquinolones can precipitate aortic complications in patients who have existing aortic disease, such as those with aortic dilatation, chronic aortic dissection, or heritable forms of aortopathy. Physicians caring for such patients need to know whether prescribing these antibiotics might cause an aortic catastrophe. This critical gap in knowledge was the impetus for our group to perform experiments using an established mouse model of sporadic aortic disease (11). In those experiments, we found that wild-type mice challenged with high-fat diet and angiotensin II infusion and exposed to ciprofloxacin had more severe aortic wall degeneration and a higher incidence of aortic aneurysm, dissection, and rupture compared with challenged control mice. Although our findings supported concerns about the drug's effects on diseased aortic wall, the absence of corroborating clinical evidence has been a barrier to influencing patient care. In this context, the new report by Chen et al. (12) in this issue of the *Journal* is timely and novel in that it represents the first clinical study demonstrating an association between fluoroquinolone exposure and aortic complications in patients with pre-existing aortic aneurysms and dissections.

SEE PAGE 1875

In this issue of the *Journal*, Chen et al. (12) used the Taiwan National Health Insurance Research Database to identify 31,570 patients who received a new aortic aneurysm or aortic dissection diagnosis during a hospital admission. During subsequent follow-up, the authors evaluated the association between outpatient fluoroquinolone exposure and major adverse

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas, USA; the Cardiovascular Research Institute, Baylor College of Medicine, Houston, Texas, USA; and the Department of Cardiovascular Surgery, Texas Heart Institute, Houston, Texas, USA.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.03.004

outcomes. To address important potential limitations, they used varied analytic designs (including self-control and active comparator), a negative control exposure (amoxicillin), 3 negative control outcomes (fracture, trauma, stroke), and sensitivity analyses. Throughout their analyses, the authors consistently found that fluoroquinolone exposure in patients with existing aortic aneurysms or dissections was associated with increased risk of all-cause death, aortic death, and both open and endovascular aortic surgery.

Several observations regarding this study point to the need for ongoing research focused on this and related areas. First, as Chen et al. (12) acknowledge, their study has several important limitations that they were not able to address through their analytic strategy. For example, the dataset does not include several important clinical variables, such as smoking, that would ideally be included in an adjusted analysis. Observational studies using administrative data will always be fraught with inherent limitations related to data quality, missing confounding variables, and opportunities for bias (10). Nevertheless, they provide essential insights about the potential relationship between fluoroquinolones and aortic disease, especially given that definitive prospective studies are not feasible for this topic. Therefore, additional observational studies—using different datasets and alternative analytic approaches—are needed to validate, complement, and build on the findings reported by Chen et al. (12).

Another area that needs investigation is the potential danger of using fluoroquinolones in patients with genetic forms of aortopathy, such as Marfan syndrome, Loeys-Dietz syndrome, and familial thoracic aortic aneurysm and dissection. In the setting of inherited defects in aortic wall integrity, fluoroquinolones might exacerbate aortic degeneration and trigger complications, even in patients who have not yet developed aortic dilatation. Like the preceding studies evaluating the general patient population, the dataset in the study by Chen et al. (12) did not include information about Marfan syndrome or related conditions, precluding subgroup analysis. Our recent experiments using a mouse model of Marfan syndrome indicated that mice exposed to ciprofloxacin had an increased risk of dissection and fatal rupture compared with control mice (13). Corroborating clinical data will be helpful in translating these concerning findings into clinical practice.

Finally, it is alarming that 24% of the patients with aortic disease in the cohort received fluoroquinolones as outpatients during follow-up. This adds to our previous finding that 20% of patients with aortic aneurysms and dissections receive fluoroquinolones during their hospital admissions (14), underscoring that future efforts to change prescribing practices will need to target both inpatient and outpatient settings. There will be a need for studies focused on designing strategies to implement evolving clinical practice recommendations and to evaluate and optimize their effectiveness.

In conclusion, the report by Chen et al. (12) represents an important contribution to the growing body of evidence supporting concerns that fluoroquinolones have a detrimental effect on the aortic wall. Further laboratory and clinical studies are clearly needed to improve our understanding of the scope of the risk and the ideal approach to changing clinical practice. In the meantime, given the life-threatening nature of the complications, it seems prudent to follow the existing FDA (15) and European Medicines Agency (16) warnings and avoid the use of these drugs in patients at risk for aortic complications, particularly those with existing aortic disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The findings described in this paper were supported in part by awards from the Roderick D. MacDonald Research Fund at Baylor St. Luke's Medical Center (17RDM004 and 18RDM001) and the National Institutes of Health (R01HL131980). Dr. LeMaire's work is supported in part by the Jimmy and Roberta Howell Professorship in Cardiovascular Surgery at Baylor College of Medicine.

ADDRESS FOR CORRESPONDENCE: Dr. Scott A. LeMaire, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, BCM 390, Houston, Texas 77030, USA. E-mail: slemaire@bcm.edu. Twitter: @scottlemaire.

REFERENCES

1. Lee CC, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med 2015;175:1839–47.

2. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015;5:e010077.

3. United States Food and Drug Administration. FDA drug safety communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Updated May 10, 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm. Accessed March 1, 2021.

4. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018;360:k678.

5. Lee CC, Lee MG, Hsieh R, et al. Oral fluoroquinolone and the risk of aortic dissection. J Am Coll Cardiol 2018;72:1369–78.

6. Vouga Ribeiro N, Gouveia Melo R, Guerra NC, et al. Fluoroquinolones are associated with increased risk of aortic aneurysm or dissection: systematic review and meta-analysis. Semin Thorac Cardiovasc Surg 2020 Nov 9 [E-pub ahead of print].

7. Newton ER, Akerman AW, Strassle PD, Kibbe MK. Association of fluoroquinolone use with short-term risk of development of aortic aneurysm. JAMA Surg 2021;156:264–72.

8. Gopalakrishnan C, Bykov K, Fischer MA, Connolly JG, Gagne JJ, Fralick M. Association of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. JAMA Intern Med 2020;180:1596–605.

9. Dong YH, Chang CH, Wang JL, Wu LC, Lin JW, Toh S. Association of infections and use of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. JAMA Intern Med 2020;180:1587–95.

10. DeGette RL, Grant RW. Observational study design challenges: the case of fluoroquinolones and aortic disease. JAMA Intern Med 2020;180:1605–6.

11. 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.

12. Chen SW, Chan YH, Wu VC, et al. Effects of fluoroquinolones on outcomes of patients with aortic dissection or aneurysm. J Am Coll Cardiol 2021;77:1875–87.

13. LeMaire SA, Zhang L, Zhang NS, et al. Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice. J Thorac Cardiovasc Surg 2020 Sep 22 [E-pub ahead of print].

14. 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.

15. United States Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics. Accessed March 1, 2021.

16. European Medicines Agency. PRAC recommendations on signals. Adopted at the 3-6 September 2018 PRAC meeting. Available at: https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-3-6-september-2018-prac-meeting_en-0.pdf. Accessed March 1, 2021.

KEY WORDS antibiotics, aortic aneurysm, aortic dissection, aortic rupture, fluoroquinolones