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## Grand Rounds: Medically Caused CAD: Fluoroquinolones

**James Demetrious, DC, DABCO**  
Diplomate, American Board of Chiropractic Orthopedists

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## James Demetrious, DC, DABCO

**Clinician**

- Active Practice >38 years
- Diplomate, American Board of Chiropractic Orthopedists
- Diplomate, International Academy of Neuromusculoskeletal Medicine

**Educator**

- Post-Grad. > 24 years
- NCMIC Speakers' Bureau for >10 years
- Northeast College of Health Sciences
- **PostGradDC**

**Honors**

- Academy of Chiropractic Orthopedists Distinguished Service and Fellow Awards
- American College of Chiropractic Orthopedists Outstanding Achievement Award

**Publications**


- Over 31 Peer-Reviewed chiropractic journal articles.
- Many Contributions to NCMIC Examiner and Podcast

**Editorial**

- Editorial Reviewer for journals *Spine*, *Annals of Internal Medicine*, and *Clinical Anatomy*
- Former Managing Editor of *Journal of Chiropractic Orthopedists*

**Community**

- Lower Cape Fear Hospice, Board Member
- Founder, Past-President Wilmington Autism Society
- Optimists Club – Safety Officer

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## Purpose...



### How about a new way to consider cervical artery dissection risk factors?

Is infection the CeAD risk factor or is it due to prescribed antibiotics?

Are migraines the CeAD risk factor or is it due to prescribed Triptans?

Do young females represent a CeAD risk factor or is it due to prescribed oral contraceptives?

~ James Demetrious, DC, DABCO



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## The Invisible Elephant in the Room...



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## CAD...Diagnostic Risk Factors

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## CAD Risk Factors?

### Factors Associated With CD:

- Major and minor cervical trauma
- Arterial hypertension
- Young age
- Current use of oral contraceptives
- Migraine
- Fibromuscular dysplasia
- Ultrastructural connective tissue abnormalities
- Vascular subtype of Ehlers-Danlos syndrome
- Marfan syndrome
- Turner syndrome
- Williams syndrome
- Familial cases
- Hereditary hemochromatosis
- Osteogenesis imperfecta type I
- $\alpha$ 1-Antitrypsin deficiency
- 677T genotype MTHFR
- Hyperhomocysteinemia
- Cystic medial necrosis of intracranial vessels
- Styloid process length
- ICAM-1 E4690 K gene polymorphism
- Autosomal-dominant polycystic kidney disease
- **Infection**
- Moyamoya disease
- Lentiginosis
- Vessel redundancies (coils, kinks, loops), especially if bilateral

Stroke. 2014;45:3155-3174.

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## CAD Risk Factors?

- **Open Neurol J. 2010; 4: 50–55. Cervical Artery Dissection: Emerging Risk Factors**
  - Primary disease of arterial wall (fibrodysplasia), Ehlers Danlos-syndrome IV, Marfan's syndrome, vessel tortuosity, **recent respiratory tract infection**, migraine, hyperhomocysteinemia, major head/neck trauma like chiropractic maneuver, coughing or hyperextension injury associated to car.
- **Lancet Neurol. 2009 Jul;8(7):668-78. Cervical-artery dissections: predisposing factors, diagnosis, and outcome.**
  - Trauma to the neck, **infection**, migraine, hyperhomocysteinaemia, underlying arteriopathy
- **Stroke. 2005 Jul;36(7):1575-80. A systematic review of the risk factors for cervical artery dissection.**
  - Aortic root diameter >34 mm, trauma, homocysteine, and **recent infection**.

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## Infection?

### Original Contribution

FREE

July 1999

## Association of Cervical Artery Dissection With Recent Infection

Armin J. Grau, MD; Tobias Brandt, MD; Florian Bugge, MD; et al

[> Author Affiliations](#) | [Article Information](#)

*Arch Neurol.* 1999;56(7):851-856. doi:10.1001/archneur.56.7.851

- In 15 (of 43 in their cohort) patients with CAD (35%) and in 5 control patients (9%;  $P=.003$ ), infection had been diagnosed and treated by physicians before dissection or ischemia.

**No other detail related to antibiotics prescribed.**



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## Infection?

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- Infection is often associated with events causing mechanical stress to cervical arteries, such as cough, vomiting, and intensive sneezing.
- However, in our multivariate analysis, a diagnosis of recent infection but not cough, sneezing, or vomiting was independently associated with CAD.
- As such mechanical factors occur frequently, they could not explain the low recurrence rate of CAD.
- Thus, mechanical stress does not sufficiently explain the association between infection and CAD.



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## Infection?

Arq Neuropsiquiatr 2005;63(2-8):523-526

### INTERNAL CAROTID ARTERY DISSECTION IN A PATIENT WITH RECENT RESPIRATORY INFECTION

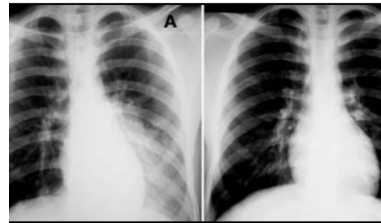
#### Case report of a possible link

Cynthia Resende Campos<sup>1</sup>, Thiago Gasperini Bassi<sup>2</sup>,  
Fabiano Pinto<sup>2</sup>, Demétrius Kasak P. Abrahão<sup>3</sup>

**ABSTRACT** - The pathogenesis of spontaneous cervical artery dissection remains unknown. Infection-mediated damage of the arterial wall may be an important triggering mechanism. We describe a 21-year-old man with respiratory infection (bronchial pneumonia) which was diagnosed and treated with antibiotic few days prior to the right internal carotid artery dissection. The patient presented ischemic retinal and cerebral strokes. Based on literature review, we discuss the possibility of a causal link between infection and arterial dissection.

**KEY WORDS:** carotid dissection, infection, stroke.

- A 21-year-old man with fever, cough and purulent sputum was diagnosed as lobar pneumonia (leukocytosis: 16.9/nL and positive chest X-ray) and treated with levofloxacin for 3 days.



Chest X-ray. A: At first admission, prior to antibiotic treatment. B: After the treatment, at the second admission.



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**KEY WORDS:** carotid dissection, infection, stroke.

- On the fourth day, pneumonia symptoms had improved, including coughing, and he was discharged.
- In the same night, he woke up with a sudden onset of intense right hemi-cranial and retroorbital pain followed by visual disturbance and left hemiplegia.
- Brain CT revealed a right striatocapsular ischemic stroke (Fig 2).
- Four-vessel digital angiography showed an irregular high-grade stenosis at the right internal carotid artery (ICA) starting about 2 cm distal to the carotid bulb extending until an occlusion into the petrous bone.
- The proximal segment of the right ICA had a tapered flame-like appearance. There was an accentuation of the filling of the external carotid artery branches (Fig 3).
- These findings supported the diagnosis of arterial dissection.

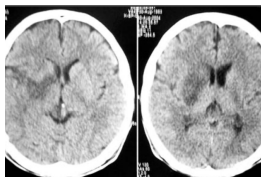


Fig 2. Brain CT: right striatocapsular ischemic stroke.



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## Infection?

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**KEY WORDS:** carotid dissection, infection, stroke.



- In conclusion, we call attention to the diagnosis of CAD as an important cause of ischemic stroke in young patients and reinforce the possibility of recent infection as an environmental trigger factor for spontaneous CAD.

**Infection???** How about iatrogenic Fluoroquinolone caused CAD?



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## Fluoroquinolones

### e-Journal

Quarterly Journal of ACO - March 2008 - Volume 5; Issue 1

### Original Articles

#### Iatrogenic Tendinopathy Associated with Levaquin (levofloxacin)

Ronald C Evans, DC, FACO, FICC

Senior Orthopedist, ICON Whole Health 1441 29<sup>th</sup> Street, Suite 100, West Des Moines, Iowa, 50266

**Figure 1.** Localized swelling at the 3-6 cm level (from the calcaneal insertion) in the left Achilles tendon.



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## Fluoroquinolones



List of FDA-Approved Systemic Fluoroquinolones

Brand Name	Active Ingredient
Avelox	moxifloxacin <sup>+</sup>
Baxdela	delafloxacin
Cipro	ciprofloxacin <sup>+</sup>
Cipro extended-release <sup>±</sup>	ciprofloxacin extended-release
Factive	gemifloxacin <sup>+</sup>
Levaquin	levofloxacin <sup>+</sup>
Ofloxacin (generic brand) <sup>±</sup>	ofloxacin

<sup>+</sup> available as brand and generic  
<sup>±</sup> available only as generic

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## Fluoroquinolones

- The FDA has added multiple black box warnings to fluoroquinolone antibiotics, a class of broad-spectrum drugs that treat bacterial infections:
  - July 2008: Increased risk of tendon rupture and tendinitis
  - February 2011: Worsening symptoms for people with myasthenia gravis
  - August 2013: Potential for irreversible peripheral neuropathy, a nerve condition that can cause pain, numbness, and weakness in the hands and feet
  - July 2016: Other serious risks, including cardiac, dermatologic, and hypersensitivity reactions

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# Fluoroquinolones

Downloaded from <http://bmjopen.bmj.com/> on October 26, 2016. Published by group: bmj.com

Open Access Research

## BMJ Open Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study

Nick Daneman,<sup>1,2,3,4</sup> Hong Lu,<sup>1</sup> Dorcas A Pocolmier<sup>1,5,6,8</sup>

**ABSTRACT**  
**Objectives:** Fluoroquinolone-associated tendon ruptures are a recognised complication, but other severe collagen-associated adverse events may also be possible. Our objectives were to confirm the association of fluoroquinolones and tendon rupture, to clarify the potential association of fluoroquinolones and retinal detachment, and to test for a potentially lethal association between fluoroquinolones and aortic aneurysms.  
**Setting:** Population-based longitudinal cohort study in Ontario, Canada.  
**Participants:** Older adults turning 65 years between April 1 1997 and March 31 2012 were followed until primary outcome, study, or end of follow-up (March 31 2012).

**Strengths and limitations of this study**

- This study reports a novel and important association of fluoroquinolone prescriptions with aortic aneurysm.
- The study design involves a population-based, longitudinal analysis of 1.7 million older adults.
- The findings are robust across multiple sensitivity, subgroup and bias analysis.
- Misclassification of fluoroquinolone exposure is possible, if some patients did not use their dispensed prescriptions.
- Identification of mild or asymptomatic aortic events is possible.

Research

Original Investigation

## Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone

Chien-Chang Lee, MD, ScD; Meng-tse Gabriel Lee, PhD; Yueh-Sheng Chen, MD; Shih-Hao Lee, MA; Yih-Shang Chen, MD, PhD; Shyh-C Tyr Chen, MD, MBA; Shan-Chwen Chang, MD, PhD

Editor's Note page 1647  
 Supplemental content at [jamainternalmedicine.com](http://jamainternalmedicine.com)

**IMPORTANCE** Fluoroquinolones have been associated with collagen degradation, raising safety concerns related to more serious collagen disorders with use of these antibiotics, including aortic aneurysm and dissection.

RESEARCH

OPEN ACCESS

## Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study

Björn Pasternak,<sup>1,2</sup> Malin Ingelmar,<sup>2,3</sup> Henrik Swanson<sup>1</sup>

**ABSTRACT**  
**OBJECTIVE:** To investigate whether oral fluoroquinolone use is associated with an increased risk of aortic aneurysm or dissection.  
**DESIGN:** Nationwide historical cohort study using linked register data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or dissection.  
**SETTING:** Sweden, July 2006 to December 2013.  
**RESULTS:** 360 088 treatment episodes of fluoroquinolone use (278 620 ciprofloxacin) and propensity score matched comparison episodes of amoxicillin use (360 088).  
**CONCLUSIONS:** In a propensity score matched cohort, fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection. The association appeared to be largely driven by aortic aneurysm.  
**INTRODUCTION:** Fluoroquinolones remain among the most commonly used antibiotics globally, and about 30 million outpatient prescriptions for fluoroquinolones were issued per year in the United States alone.<sup>1</sup> Fluoroquinolone use is associated with an increased risk of tendon disorders, including Achilles tendon rupture and tendinopathy.<sup>2</sup> The mechanisms behind these adverse events, which are recognised to a broad extent, are thought to implicate non-antimicrobial properties of



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# Fluoroquinolones

Jun and Fang *BMC Cardiovasc Disord* (2021) 21:470  
<https://doi.org/10.1186/s12872-021-02258-1>

BMC Cardiovascular Disorders

REVIEW Open Access

## Current progress of fluoroquinolones-increased risk of aortic aneurysm and dissection

Cui Jun<sup>1</sup> and Bian Fang<sup>2\*</sup>

\*Check for updates


“Of note, in December 2018, FDA issued several “black box warnings” against FQ with the latest safety announcement warning about an increased risk of ruptures in the aorta blood vessel in certain patients.”



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# Fluoroquinolones and CAD?



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## Fluoroquinolones?

**James Demetriou** <dr.demetriou@gmail.com>  
to David

Hi David,

Thank you for sending your paper to me. I am grateful for your contributions to the literature and regularly share your work in my post-grad classes as an NCMIC Speakers' Bureau member

I suspect the prevalence and commonality of fluoroquinolones and their predilection for connective tissue degradation may provide an unidentified etiology in the genesis of cervical artery dissection (CAD). A difficulty lies within the poor quality of case reports that fail to provide substantive medical histories and the identification of prior medications.

I have attached two recent papers that are of interest. Lee et al. report, "It has been demonstrated that MMPs play an important role in the pathogenesis of aortic aneurysm and dissection. Dysregulation of MMP production and activity leads to extracellular matrix degradation and medial layer degeneration." Isn't it plausible that the CADs may be likewise affected? Could this be a common but unidentified causation? Have you identified fluoroquinolones as a possible etiology to CAD in the cases you have studied? Any thoughts?

Thank you,  
Jim

**David Cassidy** Nov 29 (2 days ago)

Hi Jim:


Thanks for the papers on fluoroquinolones. I am aware of these risks, as Don Redelmeier is in the same department as me at the University of Toronto. I had not thought about cervical dissections and these medications, but yes, I do think that there could be a link and someone should study this. There is also a link between recent infection and cervical dissection, so it would be a challenge to disentangle all of these competing risks. I no longer have access to the data I used to study vertebral and carotid strokes, as the government puts a destroy data clause in contracts to use the data. Nevertheless, it would be an interesting hypothesis to test.

Thanks for you thoughts on this.

With best wishes,  
David

J. David Cassidy, PhD, DrMedSc  
Senior Scientist, Krembil Research Institute  
Toronto Western Hospital  
University Health Network

Professor, Division of Epidemiology and  
Institute of Health Policy, Management and Evaluation  
Dalla Lana School of Public Health, University of Toronto



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## My Hypothesis

Demetrius *Chiropractic & Manual Therapies* (2018) 26:22  
<https://doi.org/10.1186/s12998-018-0193-z>

Chiropractic &  
Manual Therapies

**HYPOTHESIS**

**Open Access**



### Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?

James S. Demetrius

**Conclusion:** A causal relationship of fluoroquinolone antibiotics to cervical artery dissection is plausible. The suppositions developed in this paper are insufficient to suggest that fluoroquinolones currently represent an established risk factor in the development of cervical artery dissections. Fluoroquinolones may indeed be a novel and previously unrecognized cause of cervical artery dissections.



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**HYPOTHESIS**

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### Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?

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#### Environmental risk factors

- A history of recent infection has been associated as a risk factor for cervical artery dissection [6, 7].
- Suda et al. reported an average of 24.5% more antibiotic prescriptions were dispensed in the winter months than in the summer, over a 5-year study period with a mean outpatient consumption of quinolone antibiotics of 13.66% [8].
- These combined factors may partially explain the seasonal variation and increased risk of dissection during winter months.



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**Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?**

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### Discussion

- It is plausible that fluoroquinolones may incite connective tissue degradation and play a contributory role in the genesis of cervical artery dissections.
- When considering relationships the extent of adverse effects associated with fluoroquinolones, some multifactorial, interrelated risk factors and associations warrant further investigation regarding the etiology of spontaneous cervical artery dissection:
  - **Connective tissue:** Aortic and cervical arteries are comprised of connective tissue. Fluoroquinolone toxicity is associated with connective tissue degradation and aortic aneurysms. Adverse effects of fluoroquinolone medications may explain why otherwise normal; young populations experience cervical artery dissections.
  - **Infections and seasonal relationships:** Infections are associated with an increased risk of cervical artery dissection. The frequency of infections, fluoroquinolone utilization and cervical artery dissections increase during winter months. These temporal relationships may predispose patients to iatrogenic cervical artery dissections.
  - **Latency:** The latencies of clinical manifestations following the utilization of fluoroquinolone medications require careful consideration by clinicians.
- When considering these factors, it is reasonable to ponder an associated causality between fluoroquinolone use and cervical artery dissection.

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**Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?**

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### Fluoroquinolones, aortic aneurysms, and cervical arterial dissections

- Collagen is a major extracellular matrix component of the aortic wall raising the concern that fluoroquinolones may cause or aggravate an aortic aneurysm and dissection.
- Lee et al. reported a 2- fold increase in the risk of an aortic aneurysm and dissection within 60 days of fluoroquinolone exposure [14].
- The tunica adventitia of the aortic, carotid and vertebral arteries are comprised of dense irregular connective tissue containing loosely organized collagen fibers [17].
- As fluoroquinolones may induce degradation of collagen causing aortic dissection and aneurysm, this raises the concern that fluoroquinolones may cause cervical artery dissections by a similar mechanism.

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## My Hypothesis

Demetrius *Chiropractic & Manual Therapies* 2018; 26:22  
<https://doi.org/10.1186/s12998-018-0193-z>

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### HYPOTHESIS

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## Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?

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### Conclusion

- A causal relationship of fluoroquinolone antibiotics to cervical artery dissection is plausible. Fluoroquinolones may indeed be a novel and previously unrecognized cause of cervical artery dissections.
- This hypothesis is insufficient to conclude that fluoroquinolones represent a current and established risk factor for the development of cervical artery dissections.
- An initial call for case reports and formal investigation is warranted. An extensive longitudinally observed population study might shed light upon this subject.



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## Initial Independent Confirmation

### Use of fluoroquinolones and the risk of spontaneous cervical artery dissection

E. Del Zotto<sup>a</sup> and A. Pezzini<sup>b</sup>

<sup>a</sup>U.O. Neurologia, Istituto Ospedaliero Paltambulanza, Brescia; and <sup>b</sup>Dipartimento di Scienze Cliniche e Sperimentali Clinica Neurologica, Università degli Studi di Brescia, Brescia, Italy

EUROPEAN JOURNAL OF NEUROLOGY

**Keywords:** cervical artery dissection, fluoroquinolones, ischaemic, stroke

Received 16 October 2018  
Accepted 23 January 2019

*European Journal of Neurology* 2019; 26: 1028–1031

doi:10.1111/ene.13917

**Background and purpose:** Because of their potential to alter the integrity of collagen and other components of the extracellular matrix, fluoroquinolone antibiotics might be involved in the pathogenesis of spontaneous cervical artery dissection (sCeAD).

**Methods:** In the setting of a single-centre case-control study, whether fluoroquinolone use in the 30-day period before the index event is associated with sCeAD (cases) in comparison with a group of age- and sex-matched patients who suffered a first-ever acute cerebral infarction from a cause other than CeAD (non-CeAD IS, controls) was assessed.

**Results:** Overall, 284 cases (mean age 43.2 ± 10.4 years; 58.5% men) and 568 controls qualified for the analysis. Thirty (10.6%) patients in the sCeAD group and 16 (2.8%) in the non-CeAD IS group were fluoroquinolone users ( $P \leq 0.001$ ). The use of these antibiotics was associated with a more than two-fold increased risk of sCeAD [odds ratio (OR) 2.31; 95% confidence interval (CI) 1.00–5.30] after adjusting for confounders. The risk was more substantial in the subgroup of patients with dissection involving the carotid artery (OR 2.78; 95% CI 1.14–6.78), in females (OR 4.58; 95% CI 1.04–20.1) and compared to that conferred by other antibiotics (OR 2.42; 95% CI 1.02–5.75).

**Conclusions:** Fluoroquinolones may represent a novel contributing factor involved in the pathogenesis of sCeAD.



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## Initial Independent Confirmation

**Internal Medicine**  
The Japanese Society of Internal Medicine

doi: 10.2169/internalmedicine.6736-20  
Intern Med 60: 2863-2865, 2021  
http://internmed.jp

[ CASE REPORT ]

**Vertebral Artery Dissection after Exposure to Levofloxacin:  
A Report of Two Cases**

Taku Harada<sup>1,2</sup>, Yukinori Harada<sup>2</sup> and Taro Shimizu<sup>2</sup>

**Abstract:**  
Exposure to quinolones is known to be an independent risk factor for aortic dissection; however, the association with vertebral artery dissection remains unclear. We report two cases of vertebral artery dissection that occurred 4 and 8 days after exposure to levofloxacin, respectively. Both patients had risk factors for vertebral artery dissection, and quinolone use could have been avoided. **These two cases indicate that quinolone exposure can be a risk factor for vertebral artery dissection.** Considering the possible mechanism, it is better to avoid the prescription of quinolones to patients who have insufficient connective tissues to avoid vertebral artery dissection.

**Key words:** vertebral artery dissection, quinolone, drug adverse effect

(Intern Med 60: 2863-2865, 2021)  
(DOI: 10.2169/internalmedicine.6736-20)

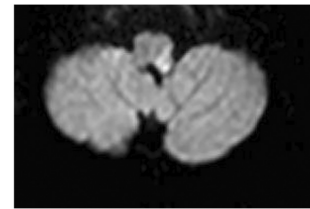
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## Initial Independent Confirmation

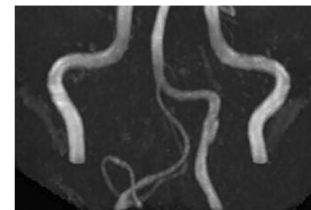
### Case 1

- A 45-year-old man presented to the emergency department with sudden-onset left posterior neck pain and left hemiparesis.
- His medical history included hypertension, dyslipidemia, and diabetes mellitus, and he had taken levofloxacin orally for a sore throat and cough for 8 days.
- He had no history of connective tissue disease or head and neck trauma.
- His vital signs were normal, except for high blood pressure (152/95 mmHg).
- A neurological examination revealed nystagmus, left hemifacial hypoalgesia, left-sided deficit of cranial nerves VII, IX, and X and paralysis of the left upper limb.
- Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) of the brain revealed left vertebral artery dissection and infarction of the left medulla (Fig. 1, 2).
- A diagnosis of Wallenberg syndrome associated with vertebral artery dissection was made.
- He received conservative therapy and was subsequently transferred to a rehabilitation hospital on day 30. He had a Modified Rankin Scale score of 3.

Intern Med 60: 2863-2865, 2021



**Figure 1.** On diffusion-weighted magnetic resonance imaging, the left lateral medulla showed a high signal intensity.



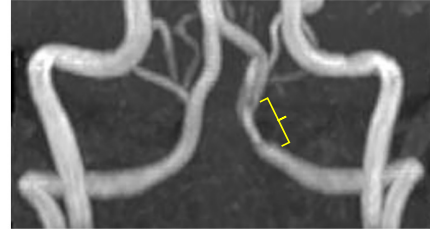
**Figure 2.** Magnetic resonance angiography showed dilation of the left vertebral artery with irregularity.

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## Initial Independent Confirmation

### Case 2

- A 66-year-old man was transferred to the hospital for the treatment of pancreatitis with pancreatic abscess.
- He developed pneumonia and was initially treated with intravenous levofloxacin on postoperative day 9.
- He developed sudden-onset left occipital pain on postoperative day 13.
- MRI/MRA performed on postoperative day 17 revealed left vertebral artery dissection (Fig. 3).
- His vital signs were normal, with no neurologic abnormalities, and
- MRI showed no complications of ischemic stroke.
- The administration of levofloxacin was continued until postoperative day 30. The patient was discharged on postoperative day 35 with no neurological complications.



**Figure 3.** Magnetic resonance angiography showed dilatation of the left vertebral artery with focal stenosis.

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## Initial Independent Confirmation

- There are several possible mechanisms through which quinolones may cause arterial dissection:
  - Quinolones have properties, such as chelation of several metal ions (e.g., calcium, magnesium, and aluminum), which are essential for type 1 collagen synthesis (1),
  - The decreased expression and activity of lysyl oxidase, and the increased expression and activity of matrix metalloproteinases (1, 5).
    - Type 1 collagen is a major component of the vessel wall (6), and a decrease of type 1 collagen may lead to vessel wall vulnerability.
    - The lysyl oxidases are extracellular copper enzymes that initiate the crosslinking of collagens and elastin.
    - These crosslinks provide the tensile strength and elastic properties of vascular walls.
    - Some reports indicated that decreased expression of lysyl oxidase can be associated with vulnerability of arteries (7), which can result in aortic dissection and aneurysm (8).
  - Matrix metalloproteinases are a family of proteolytic enzymes that degrade several components of the extracellular matrix and which mediate vascular remodeling, which may cause vascular dissection. In fact, increase serum levels of matrix metalloproteinase-9 have been reported to be associated with vertebral artery dissection (9).

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## Initial Independent Confirmation

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### Fluoroquinolone use preceding medium-size artery dissection: A case series



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**Conclusion** In addition to the well-recognized risk of aortic dissection following FQ use, visceral arterial dissection should also be considered if abdominal pain occurs, as it is likely in our case series. To our knowledge, it is the first case series reporting visceral artery dissections following a treatment by FQ. All the previous studies establishing a link between arterial dissection and FQ were related to aortic syndrome or carotid arteries. Although this class of antibiotics is effective to treat many infectious diseases, their prescription must be earmarked for weighed medical indications and avoided in patients with a previous history of dissection or underlying condition of arterial fragility. In addition, the search for a fluoroquinolone intake must be carried out precisely in the event of the discovery of a medium-sized arterial dissection.

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## Follow-Up...

### Risk of Intracranial Aneurysm and Dissection and Fluoroquinolone Use A Case-Time-Control Study

Sandy Maumus-Robert<sup>1</sup>, PharmD, PhD; Stéphanie Debette, MD, PhD; Xavier Bérard, MD, PhD; Yohann Mansiaux, PhD; Pascale Tubert-Bitter, PhD; Antoine Pariente, MD, PhD

**Background and Purpose**—Fluoroquinolone use is associated with an increased risk of aortic aneurysm and dissection. We investigated this risk of arterial wall injury on intracranial arteries, given the similar pathophysiological mechanisms for aneurysm and dissection in both types of arteries.

**Methods**—A case-time-control study was conducted using French National Insurance databases covering >60 million inhabitants. Cases were aged ≥18 years with first ruptured intracranial aneurysm and dissection between 2010 and 2015. For each case, fluoroquinolone use was compared between the exposure-risk window (day 30–day 1 before the outcome) and matched control windows (day 120–day 91, day 150–day 121, and day 180–day 151) and adjusted for time-varying confounders; potential time-trend for exposure was controlled using an age- and sex-matched reference group. Amoxicillin use was studied similarly for indication bias controlling. The potential excess of risk conveyed by fluoroquinolones was assessed by the ratio of OR for fluoroquinolones to that for amoxicillin.

**Results**—Of the 7443 identified cases, 75 had been exposed to fluoroquinolones in the prior 180 days, including 16 in the 30-day at-risk window (385/97 cases exposed to amoxicillin, respectively). The adjusted OR for fluoroquinolones was 1.26 (95%CI, 0.65–2.41) and that for amoxicillin of 1.36 (95% CI, 1.05–1.78). Ratio of OR for fluoroquinolones to that for amoxicillin was estimated at 0.92 (95% CI, 0.46–1.86). Result was similar when extending outcome definition to unruptured events (ratio of OR for fluoroquinolones to that for amoxicillin, 0.97 [95% CI, 0.61–1.53]).

**Conclusions**—This study did not evidence an excess of risk of intracranial aneurysm or dissection with fluoroquinolone use. (*Stroke*. 2020;51:994–997. DOI: 10.1161/STROKEAHA.119.028490.)

**Key Words:** amoxicillin ■ fluoroquinolones ■ intracranial aneurysm ■ intracranial arterial diseases ■ pharmacoepidemiology ■ subarachnoid hemorrhage

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## Some Citations...

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Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

Journal homepage: [www.elsevier.com/locate/jocn](http://www.elsevier.com/locate/jocn)

**Vertebrobasilar and internal carotid arteries dissection in 188 patients**

Biljana Georgievski Brkić<sup>a</sup>, Tatjana Dučić Jaramaz<sup>b</sup>, Marjana Vukičević<sup>c</sup>, Nataša Stanislavljević<sup>d</sup>, Dejan Kostić<sup>e</sup>, Miloš Lučić<sup>f</sup>, Ivan Marinković<sup>g</sup>, Tija Apostolović<sup>h</sup>, Tatjana Vlašković<sup>i</sup>, Ana Ćirković<sup>j</sup>, Slobodan Marinković<sup>k</sup>

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<sup>j</sup> Department of Neuroanatomy, Institute of Anatomy, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

skull base surgery [49,55,84]. Certain types of medication can occasionally produce dissections [50,54,85], then arterial elongation [60], fibromuscular dysplasia and connective tissue diseases [8,12,42,86–88], polycystic kidney disease, pregnancy and postpartum [89–91], as well as certain gene mutations [9,86,92–94].

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## Some Citations...

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Journal of Clinical Neuroscience

Journal homepage: [www.elsevier.com/locate/jocn](http://www.elsevier.com/locate/jocn)

Case report

**Unilateral common carotid artery dissection in a patient with recent COVID-19: An association or a coincidence?**

Omur Serdar Gençler<sup>a,\*</sup>, Meltem Refikler Ege<sup>b</sup>, Aydın Aslan<sup>c</sup>

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**ABSTRACT**

The "Corona Virus Disease 2019 (COVID-19)", caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), progressed rapidly since its first outbreak, and quickly developed into a pandemic. Although COVID-19 mostly presents with respiratory symptoms, researchers have started reporting neurologic manifestations such as cerebrovascular diseases in patients with COVID-19 as the pandemic has progressed. Herein, we report a case of 58-year-old female patient identified with a left common carotid artery dissection, with COVID-19. Clinicians must keep in mind that COVID-19 can cause vascular complications such as carotid artery dissections in the ensuing period, even after the acute phase, although there is currently a lack of sufficient evidence to identify any causal association between COVID-19 and arterial dissections.

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"It was understood that the patient had presented to an external facility with complaints of fever and fatigue approximately 1 month earlier, and had received therapy after being diagnosed with COVID-19."

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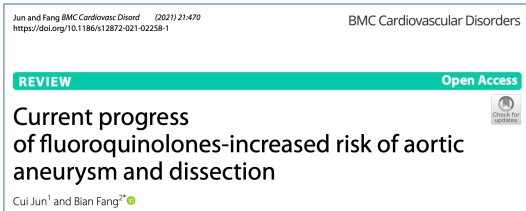


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## Mechanisms of FQ Damage



- Some hypothesized biological mechanisms have been proposed:
  - FQ may interfere with ECM integrity in the aortas.
  - Dysregulation of ECM homeostasis disrupted ECM integrity and impaired biomechanical strength, which finally triggered progressive aortic weakening, dissection, or rupture [55].
  - Enzymatic degradation of ECM by MMPs and vascular remodeling constituted the most prominent characters of AA [56].
  - FQ reduced collagen production in tenocytes [57] and fibroblasts [58].
  - Ciprofloxacin (the most commonly used FQ) suppressed TIMP-1 expression but enhanced MMP expression in the cornea [59], in tendon cells and tissues [57, 60], and in fibroblasts [61], which finally promoted MMP activation and tissue destruction.

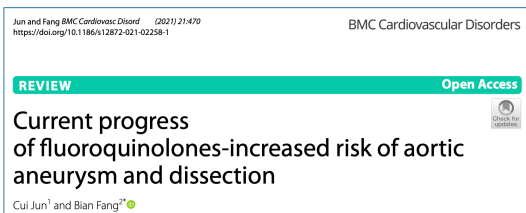


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## Mechanisms of FQ Damage



- It was suggested that ciprofloxacin greatly up-regulated MMP activity more than twofold in cultured human aortic smooth muscle cells (HSMCs) [62].
- Human aortic fibroblasts exposed to FQ showed an increased capacity for ECM dysregulation by reducing the expression of collagen and endogenous pro-tease inhibitors protein.
- They further demonstrated collagen degradation and decreased TIMPs activity in human aortic fibroblasts cultured with 2 days FQ [63].
- A recent study confirmed that ciprofloxacin significantly increased the incidence of AAD (79%) in mice [47].

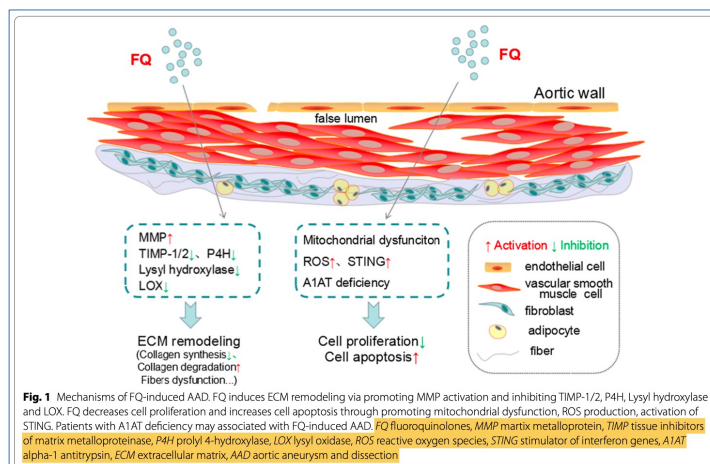


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## Mechanisms of FQ Damage



Jun and Fang *BMC Cardiovasc Disord* (2021) 21:470

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## Further Study...

Jun and Fang *BMC Cardiovasc Disord* (2021) 21:470  
https://doi.org/10.1186/s12872-021-02258-1

BMC Cardiovascular Disorders

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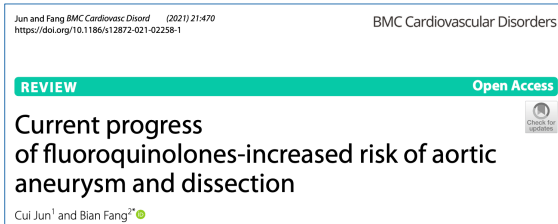
Current progress of fluoroquinolones-increased risk of aortic aneurysm and dissection

Cui Jun<sup>1</sup> and Bian Fang<sup>2\*</sup>

- Population-based studies reported an annual incidence of AA of 3–13.7/100,000 population, and AD of 3–20/100,000 population [2–4].
- Over the past decades, it is suggested that the rate of mortality from AA and AD has risen ranging from 1.2 to 24.8 fold in many developed countries, such as the United States, Britain and Japan [6, 7].
- Fluoroquinolones (FQ) are the most widely used pre-scribed antibiotics in the world. In the United States alone, about 30 million outpatient prescribed with FQ per year [9].
- FQ shows activity against both Gram-positive and Gram-negative bacteria, and are widely used to treat skin, urinary tract, bone, soft tissue, pulmonary infections and so on.

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## Further Study...



- **FQ are classified into 5 categories:**

- 1st generation FQ include nalidixic acid, oxolinic acid, piperidic acid and rosoxacin.
- 2nd generation FQ contain ciprofloxacin, norfloxacin, enoxacin, pefloxacin, lomefloxacin, nadifloxacin, rufloxacin, and ofloxacin.
- 3rd generation FQ contain levofloxacin, pazufloxacin, temafloxacin, tosufloxacin, sparfloxacin, gre- pafloxacin, and balofloxacin
- 4th generation FQ include prulifloxacin, trovafloxacin, alatrofloxacin, delafloxacin, clinafloxacin, besifloxacin, sitafloxacin, finafloxacin, gatifloxacin, gemi- floxacin, and moxifloxacin
- 5th generation FQ include lev- onadifloxacin, nemonoxacin (non-fluorinated quinolone antibiotic), and zabofloxacin

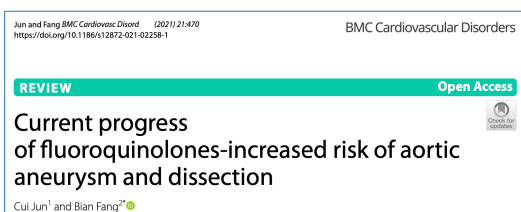


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## Further Study...



- The most common AEs of FQ are mild and reversible, like headaches, diarrhea and nausea. However, we should pay more attention to **FQ-related serious AEs**, such as:
  - tendinitis and tendon rupture,
  - hepatic toxicity,
  - *Clostridium difficile* infections,
  - prolonged QT interval,
  - torsades de pointes (ventricular tachycardia),
  - phototoxicity,
  - dysglycemia,
  - acute renal failure and
  - seizures [23, 24]
  - arrhythmia (85% increase) and cardiovascular mortality (71% increase).
  - In December 2018, FDA issued several "black box warnings" against FQ about an increased risk of ruptures in the aorta blood vessel in certain patients.

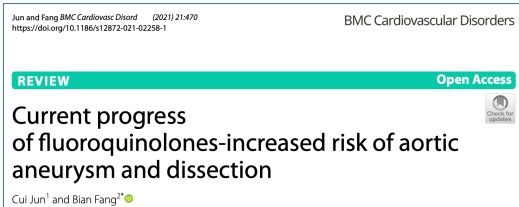


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## Further Study...



- Numerous studies have highlighted the critical roles of smooth muscle function and extracellular matrix (ECM) (collagen and elastic fibers) in structural integrity of the arterial wall.
- Collagen and elastic fibers play important roles in the mechanical properties of the vessel wall.
- At the pathological level, TAA is characterized by medial degeneration, including:
  - elastic fibers fragmentation and loss of elastic tissue,
  - vascular smooth muscle cells (VSMCs) loss, defects in collagen microarchitecture,
  - proteoglycan deposition and a less remarkable inflammatory cells infiltration.
- Moreover, three important pathological marks are displayed in the progression of AAA:
  - ECM degradation,
  - VSMCs loss and
  - infiltration of macrophages, neutrophils, mast cells and T/B lymphocytes.

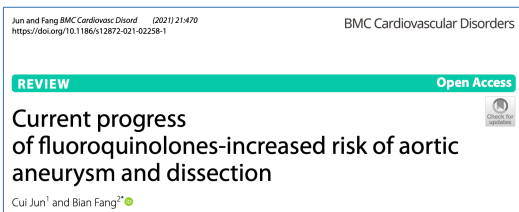


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## Duration of FQ Use



- Lee et al. [1] found an increased risk in AAD with FQ use (rate ratio [RR]=2.43; 95% confidence interval [CI]=1.83–3.22).
- Revealed a twofold increase the risk of AAD after FQ exposure.
- Oral FQ were associated with increased incidence of aneurysm formation in United States adults.



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## Duration of FQ Use

Jun and Fang *BMC Cardiovasc Disord* (2021) 21:470  
<https://doi.org/10.1186/s12872-021-02258-1>

BMC Cardiovascular Disorders

REVIEW Open Access

**Current progress of fluoroquinolones-increased risk of aortic aneurysm and dissection**

Cui Jun<sup>1</sup> and Bian Fang<sup>2\*</sup>

Check for updates

- Current FQ use within 60 days was associated with the highest risk of AAD.
- Increased risk of AAD with prolonged FQ use.
- Higher risk of AAD was associated with FQ exposure for longer than 14 days.
- However, recent results indicated that FQ were associated with increased 90-day incidence of:
  - AAA (HR=1.31; 95% CI 1.25–1.37),
  - iliac artery aneurysm (HR = 1.60; 95% CI 1.33–1.91),
  - and other AAA (HR=1.58; 95% CI 1.39–1.79) [41].
- Of note, the investigator suggested that FQ should be used with caution in adults, not just in high-risk individuals [41].



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## Latencies...

Demetrious *Chiropractic & Manual Therapies* (2018) 26:22  
<https://doi.org/10.1186/s12998-018-0193-z>

Chiropractic & Manual Therapies

HYPOTHESIS Open Access

**Spontaneous cervical artery dissection: a fluoroquinolone induced connective tissue disorder?**

James S. Demetrious

CrossMark

### Fluoroquinolone latency

- A considerable latency from the commencement of fluoroquinolones to the onset of symptoms have been attributed to delayed mitochondrial toxicity, depletion, mutation, and cytotoxicity providing a foundation for reported occurrence of associated adverse effects [12].
- In a review of 98 case reports of fluoroquinolone-associated tendinopathy, symptoms were reported as occurring within two hours of taking the medication to as long as six months after the cessation of treatment, with the median time of onset of six days [13].
- The FDA reports that side effects occurred within hours to weeks after starting the fluoroquinolone, for an average of fourteen months to as long as nine years after stopping the medicines.
- Several cases reported that some side effects stopped or improved after discontinuation of the drug; others reported the side effects worsened or continued [9].



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## Questions?

- Any clinical experience with FQs in your office?
- Thoughts about contributing predispositions that may produce the perfect storm?
- Are FQ's a CeAD risk factor?
- Decision making?
- Recommendations?
- New research?



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November - TBA - Cervical Artery Dissection (5 CE Hour)  
December - TBA - Cervical Artery Dissection (5 CE Hour)

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## Upcoming Grand Rounds Schedule



### The First Tuesday of the Month at 8PM EST

#### Upcoming Rounds

- **July 2, 2024 – Modic Changes**
- **Additional live qualifying CAD classes will be available at the end of the year.**

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## Thank you!



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