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Adverse effects of fluoroquinolones – dysglycemia, QT prolongation and aortic dissection

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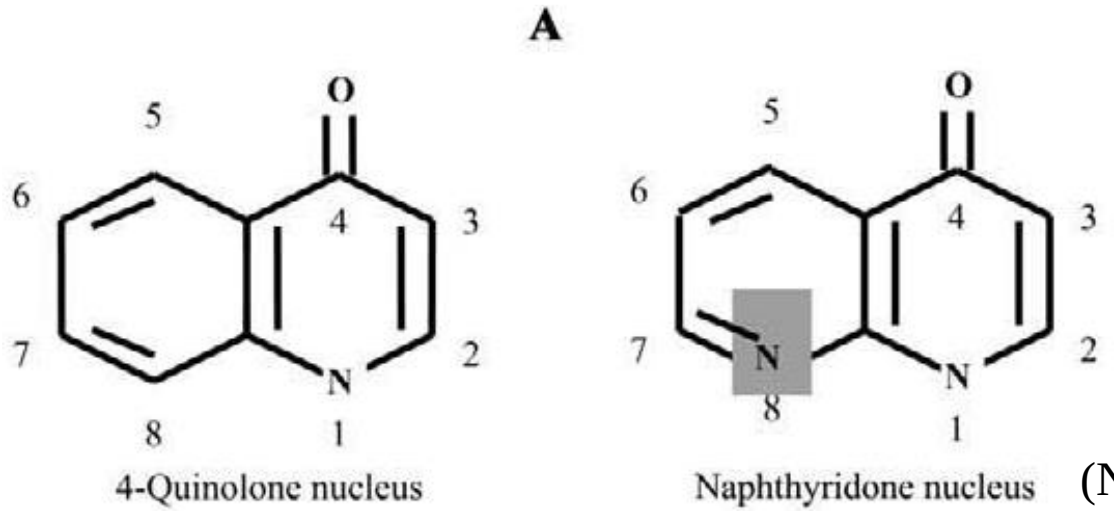
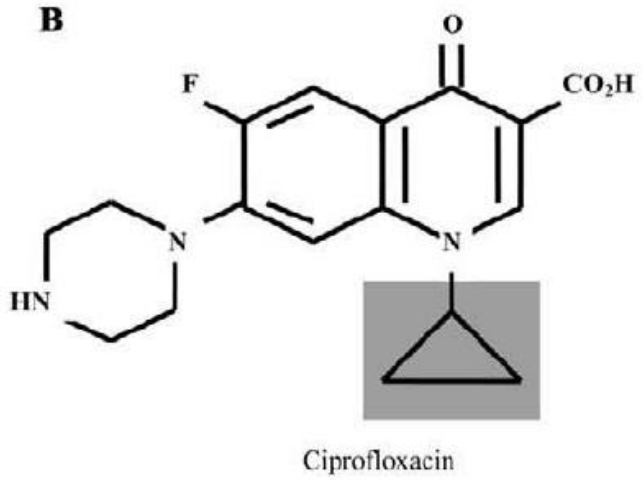
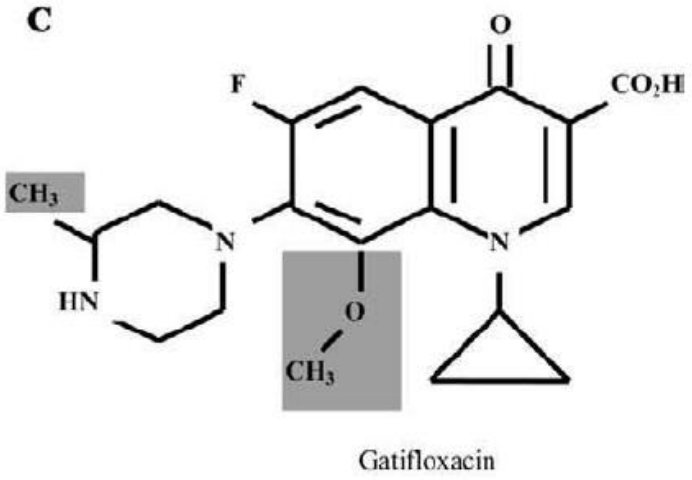
Antimicrobial Safety: Fluoroquinolones



(Nalidixic acid, gemifloxacin)





Clin Infect Dis 2005; 41:S144–57

Antimicrobial Safety: Fluoroquinolones

- The most common adverse events associated with the quinolone class: the gastrointestinal tract (nausea and diarrhea) and central nervous system (CNS) (headache and dizziness).

- Uncommon and potentially serious adverse events: the cardiovascular system (electrocardiographic QT interval prolongation), musculoskeletal system (tendinitis and tendon rupture), endocrine system (glucose homeostasis dysregulation), renal system (crystalluria, interstitial nephritis, and acute renal failure), and the CNS (seizures).

Clin Infect Dis 2005; 41:S144–57

Antimicrobial Safety: Fluoroquinolones

- Phototoxicity, Anaphylaxis, Clostridium difficile–associated diarrhea.
- Severe idiosyncratic adverse events are specific to individual agents that may share some structural congruity, such as the 1-(2,4)-difluorophenyl group shared by trovafloxacin (associated with hepatitis), temafloxacin (associated with hemolytic-uremic syndrome), and tosufloxacin (associated with eosinophilic pneumonitis).
- Quinolones with higher discontinuation rates, such as trovafloxacin (7.0%) and grepafloxacin (6.4%), are no longer available for general use.

Clin Infect Dis 2005; 41:S144–57

Fluoroquinolones : gastrointestinal toxicities

- GI toxicities have included, nausea, anorexia, vomiting, abdominal pain, diarrhea, and taste disturbance. The incidences of these toxicities generally are 2%–20%.

- No correlation between chemical structure and GI toxicity.

Clin Infect Dis 2005; 41:S144–57

Fluoroquinolones : CNS adverse reactions

- Overall incidence of CNS symptoms : 1%–2%.
- More commonly reported symptoms: dizziness, headache, and somnolence.
- less commonly reported: agitation, delirium, confusion, acute organic psychosis, and abnormal vision.
- Rare: seizure
  - association between the similar chemical structures of certain substituents at position 7 of the quinolone nucleus and the chemical structure of g-aminobutyric acid (GABA)
  - lomefloxacin—that contains a substituted piperazine group at position 7 and has been linked to seizures
  - Gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin lack the specific structure-toxicity relationships noted to induce seizures

Clin Infect Dis 2005; 41:S144–57

Fluoroquinolones : dysglycemia

- The quinolones, as a class, have demonstrated the capacity to close K^+-ATP channels in the pancreatic β cell, resulting in release of insulin and subsequent hypoglycemia.
- Product labels for ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin mention the possibility of hypoglycemia and hyperglycemia, whereas that for gemifloxacin mentions hyperglycemia only.
- CYP drug interactions do not explain interactions that would result in pharmacokinetic changes in most medications used to treat type 2 diabetes. Of the quinolones, only ciprofloxacin, clinafloxacin, enoxacin, grepafloxacin, pefloxacin, and tosufloxacin inhibit CYP 1A4 isoenzymes

Clin Infect Dis 2005; 41:S144–57

Gatifloxacin and dysglycemia

- In postmarketing studies of gatifloxacin for the treatment of respiratory tract infections, associations with hyperglycemia were rare and were increased in elderly patients
  - age <65 years, <0.1%;
  - age 65–79 years, 0.2%;
  - age 80 years, 0.6%.

- In patients with diabetes treated with gatifloxacin, the overall incidence of hypoglycemia was 0.4%, 0.7%, and 1.6% for patients <65, 65–69, and 80 years old, respectively; corresponding incidences of hyperglycemia were 1.0%, 1.6%, and 3.3%, respectively.

Diagn Microbiol Infect Dis 2002; 44:109–16

Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults

- Two population-based, nested case–control studies.
- In the first, case patients were persons treated in the hospital for hypoglycemia after outpatient treatment with a macrolide, a second-generation cephalosporin, or a respiratory fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin, or ciprofloxacin).
- In the second, case patients were persons who received hospital care for hyperglycemia. For each case patient, we identified up to five controls matched according to age, sex, the presence or absence of diabetes, and the timing of antibiotic therapy.

N Engl J Med 2006;354:1352-61

Association between Hypoglycemia-Related Hospital Visits and Recent Antibiotic Use in Older Adults

Variable	Case Patients	Controls	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
	no. (%)			
All patients	**788**	**3791**		
Fluoroquinolones				
Gatifloxacin	61 (7.7)	77 (2.0)	4.4 (3.0–6.3)	4.3 (2.9–6.3)
Levofloxacin	114 (14.5)	341 (9.0)	1.7 (1.4–2.2)	1.5 (1.2–2.0)
Moxifloxacin	24 (3.0)	162 (4.3)	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Ciprofloxacin	209 (26.5)	1075 (28.4)	1.1 (0.9–1.3)	0.9 (0.8–1.1)
Cephalosporins†	62 (7.9)	397 (10.5)	0.9 (0.6–1.2)	0.9 (0.6–1.2)
Macrolides‡	318 (40.4)	1739 (45.9)	1.0	1.0

N Engl J Med 2006;354:1352-61

Association between Hypoglycemia-Related Hospital Visits and Recent Antibiotic Use in Older Adults

Variable	Case Patients	Controls	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
	no. (%)			
Patients with diabetes	**724**	**3473**		
Fluoroquinolones				
Gatifloxacin	57 (7.9)	73 (2.1)	4.3 (2.9–6.2)	4.2 (2.8–6.3)
Levofloxacin	104 (14.4)	307 (8.8)	1.8 (1.3–2.3)	1.5 (1.2–2.0)
Moxifloxacin	22 (3.0)	149 (4.3)	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Ciprofloxacin	195 (26.9)	1002 (28.9)	1.1 (0.9–1.3)	0.9 (0.7–1.1)
Cephalosporins†	55 (7.6)	362 (10.4)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Macrolides‡	291 (40.2)	1580 (45.5)	1.0	1.0
Patients without diabetes	**64**	**318**		
Fluoroquinolones				
Gatifloxacin	<6	<6	6.4 (1.4–29.9)	9.0 (1.3–63.4)
Levofloxacin	10 (15.6)	34 (10.7)	1.7 (0.7–3.9)	2.1 (0.7–6.0)
Moxifloxacin	<6	13 (4.1)	1.0 (0.2–4.5)	1.7 (0.2–11.8)
Ciprofloxacin	14 (21.9)	73 (23.0)	1.1 (0.6–2.3)	1.2 (0.5–2.9)
Cephalosporins†	7 (10.9)	35 (11.0)	1.2 (0.5–3.0)	2.3 (0.8–6.7)
Macrolides‡	27 (42.2)	159 (50.0)	1.0	1.0

Association between Hyperglycemia-Related Hospital Visits and Recent Antibiotic Use in Older Adults

Variable	Case Patients	Controls	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
	no. (%)			
All patients	**470**	**2280**		
Fluoroquinolones				
Gatifloxacin	86 (18.3)	42 (1.8)	16.3 (10.4–25.4)	16.7 (10.4–26.8)
Levofloxacin	52 (11.1)	233 (10.2)	1.6 (1.1–2.3)	1.3 (0.9–1.9)
Moxifloxacin	20 (4.3)	70 (3.1)	2.0 (1.2–3.5)	1.7 (1.0–3.0)
Ciprofloxacin	113 (24.0)	576 (25.3)	1.4 (1.0–1.8)	1.1 (0.9–1.5)
Cephalosporins†	38 (8.1)	235 (10.3)	1.2 (0.8–1.7)	1.2 (0.8–1.7)
Macrolides‡	161 (34.3)	1124 (49.3)	1.0	1.0

N Engl J Med 2006;354:1352-61

Association between Hyperglycemia-Related Hospital Visits and Recent Antibiotic Use in Older Adults

Variable	Case Patients	Controls	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Patients with diabetes	**292**	**1403**		
Fluoroquinolones				
Gatifloxacin	59 (20.2)	25 (1.8)	22.7 (12.4–41.4)	23.6 (12.4–44.6)
Levofloxacin	31 (10.6)	129 (9.2)	1.9 (1.2–2.9)	1.6 (1.0–2.5)
Moxifloxacin	9 (3.1)	40 (2.9)	2.0 (0.9–4.3)	1.7 (0.8–3.9)
Ciprofloxacin	83 (28.4)	393 (28.0)	1.6 (1.1–2.2)	1.3 (0.9–1.8)
Cephalosporins†	20 (6.8)	149 (10.6)	1.0 (0.6–1.7)	1.0 (0.6–1.7)
Macrolides‡	90 (30.8)	667 (47.5)	1.0	1.0
Patients without diabetes	**178**	**877**		
Fluoroquinolones				
Gatifloxacin	27 (15.2)	17 (1.9)	9.9 (5.0–19.5)	12.8 (5.9–27.8)
Levofloxacin	21 (11.8)	104 (11.9)	1.4 (0.8–2.3)	1.0 (0.5–1.8)
Moxifloxacin	11 (6.2)	30 (3.4)	2.2 (1.0–4.6)	1.6 (0.7–3.9)
Ciprofloxacin	30 (16.9)	183 (20.9)	1.1 (0.7–1.7)	0.9 (0.6–1.6)
Cephalosporins†	18 (10.1)	86 (9.8)	1.4 (0.8–2.5)	1.5 (0.8–2.7)
Macrolides‡	71 (39.9)	457 (52.1)	1.0	1.0

Editorial
Serious Adverse Drug Effects — Seeing the Trees through the Forest

- Gatifloxacin now takes its place among an ever-growing list of medications that have been associated with very serious adverse effects. The most immediate question is what should be done with gatifloxacin. It seems clear that the drug's place among broad-spectrum antibiotics available for outpatient use is tenuous at best. For every approved indication for gatifloxacin, there are safer, equally effective, and less costly alternatives.

N Engl J Med 2006;354;13:1413

Risk of Severe Dysglycemia Among Diabetic Patients Receiving Levofloxacin, Ciprofloxacin, or Moxifloxacin in Taiwan

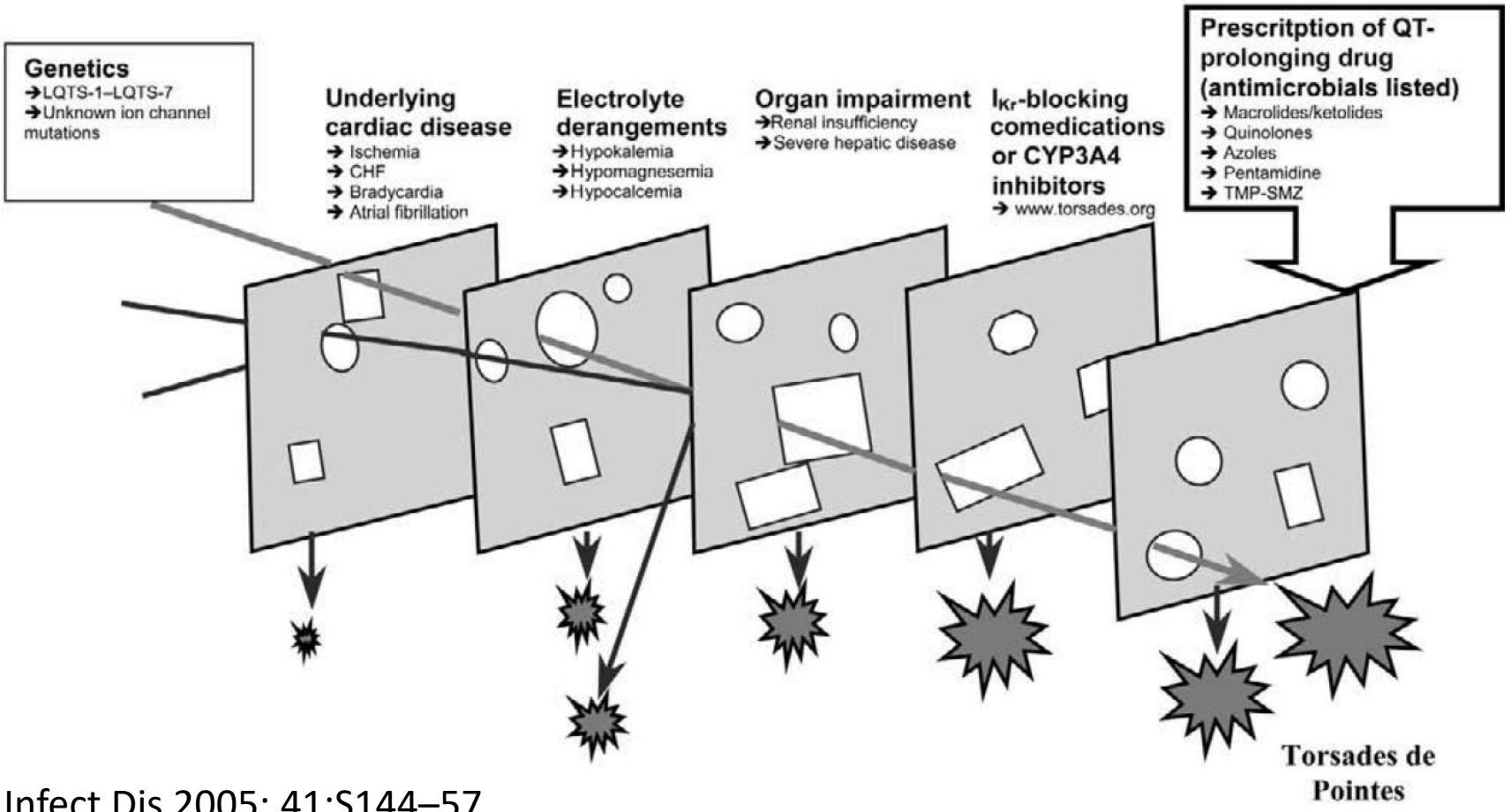
Antibiotic Group	No.	Events	Incidence (‰)	Adjusted OR (95% CI)
Hyperglycemia				
Macrolides	29 565	48	1.62	1.00
Cephalosporins	20 317	42	2.07	1.36 (.87–2.13)
Moxifloxacin	4221	29	6.87	2.48 (1.50–4.12)
Levofloxacin	11 766	46	3.91	1.75 (1.12–2.73)
Ciprofloxacin	12 564	50	3.98	1.87 (1.20–2.93)
Hypoglycemia				
Macrolides	29 565	110	3.72	1.00
Cephalosporins	20 317	65	3.20	0.94 (.68–1.32)
Moxifloxacin	4221	42	9.95	2.13 (1.44–3.14)
Levofloxacin	11 766	109	9.26	1.79 (1.33–2.42)
Ciprofloxacin	12 564	99	7.88	1.46 (1.07–2.00)

Abbreviations: CI, confidence interval; OR, odds ratio.

Clin Infect Dis 2013;57(7):971–80

QTc interval prolongation and TdP

- The blockade of the rapid component of the delayed rectifier K^+ current (IKr)



Clin Infect Dis 2005; 41:S144–57

Table 2. Adverse events considered to be surrogates for arrhythmias from comparative phase 2/3 studies.

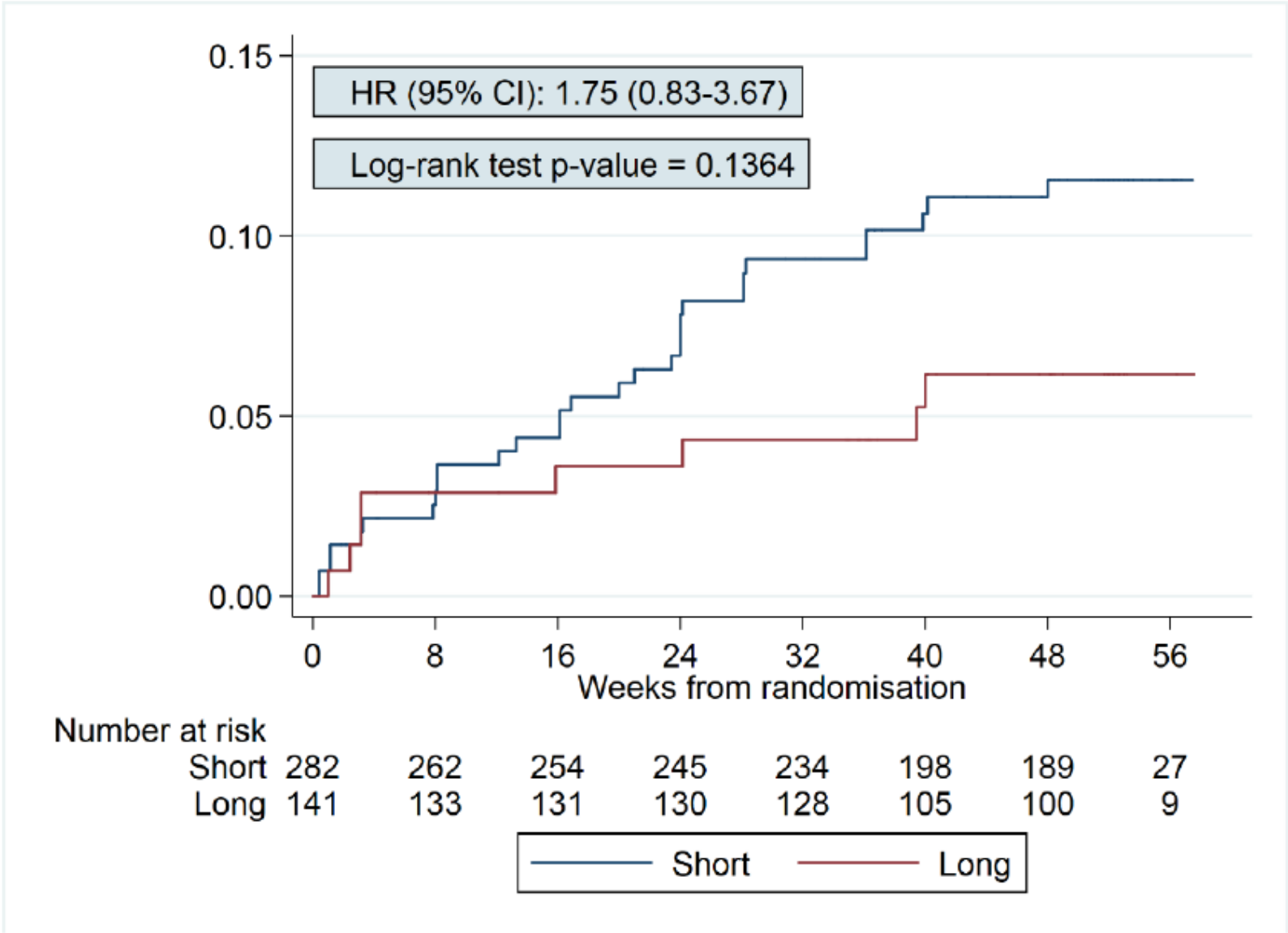
	Studies of oral moxifloxacin		Studies of intravenous moxifloxacin	
Adverse event	Oral moxifloxacin (n = 5407)	Comparators[a] (n = 5097)	Intravenous moxifloxacin (n = 550)	Comparators[a] (n = 579)
Chest pain	42 (0.8)	35 (0.7)	16 (2.9)	13 (2.3)
Tachycardia	24 (0.4)	19 (0.4)	8 (1.5)	8 (1.4)
Hypotension	19 (0.4)	21 (0.4)	11 (2.0)	8 (1.4)
Palpitation	13 (0.2)	11 (0.2)	…	…
Atrial fibrillation	13 (0.2)	2 (<0.1)	11 (2.0)	10 (1.7)
Congestive heart failure	11 (0.2)	9 (0.2)	14 (2.6)	13 (2.3)
Angina pectoris	11 (0.2)	1 (<0.1)	0 (0.0)	4 (0.7)
Syncope	9 (0.2)	10 (0.2)	2 (0.4)	2 (0.3)
Arrhythmia	4 (<0.1)	3 (<0.1)	2 (0.4)	4 (0.7)
QT interval prolongation	4 (<0.1)	1 (<0.1)	7 (1.3)	4 (0.7)
Myocardial infarction	1 (<0.1)	5 (0.1)	2 (0.4)	6 (1.0)
Abnormal ECG	…	…	5 (0.9)	3 (0.5)
Ventricular tachycardia	…	…	…	1

NOTE. Data are no. (%) of patients. Data were derived from Ball et al. [32]. ECG, electrocardiogram.

[a] Levofloxacin, trovafloxacin, and amoxicillin-clavulanate, with or without clarithromycin.

Clin Infect Dis 2005; 41:S144–57

Kaplan-Meier plot of time to exceeding maximum in QT or QTcF to 500ms or above post baseline



N Engl J Med 2019 DOI: 10.1056/NEJMoa1811867

INT J TUBERC LUNG DIS 20(9):000–000

http://dx.doi.org/10.5588/ijtld.15.0884

1969 - 2019

PERSPECTIVE

Gatifloxacin for short, effective treatment of multidrug-resistant tuberculosis

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1969 - 2019

AGORA
CORRESPONDENCE

Should gatifloxacin be included in the model list of essential medicines?

Chiang C-Y, Trébucq A, Piubello A, et al. Eur Respir J 2018; 51: 1702329 [https://doi.org/10.1183/13993003.02329-2017].

Fluoroquinolones : arthropathies and tendinitis

- Arthropathy usually presents as pain, stiffness, and swelling of the involved joints within the first few days of therapy and resolves within days to weeks after discontinuation of therapy.
- levofloxacin and pefloxacin being associated with more reports than were ciprofloxacin, enoxacin, moxifloxacin, and rufloxacin
- quinolone-associated tendinitis and tendon rupture, primarily affecting the Achilles tendon, as well as cases occurring in the shoulders and hands.
- In up to 50% of patients, symptoms appear bilaterally. Symptoms emerge, on average, 13 days after initiation of quinolone therapy (range, 1–152 days) and may not subside for 12 months after discontinuation

Clin Infect Dis 2005; 41:S144–57

Aortic aneurysm (AA), and aortic dissection(AD)

- AA/AD are among the deadliest cardiovascular diseases
- Population-based studies reported an annual incidence of AA of 3 to 13.7 per 100,000 population, and AD of 3 to 20 per 100,000 population.
- The annual incidence of AA for the elderly population is reported to be much higher at 130 per 100,000 population.
- Risk factors: Aortic wall defects and prolonged hypertension, old age, male sex, atherosclerotic disease and congenital disorders with collagen defects such as Marfan or vascular Ehlers-Danlos syndromes.

J Am Coll Cardiol 2018;72:1369–78

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

- A nested case-control analysis of 1477 case patients and 147 700 matched control cases from Taiwan's National Health Insurance Research Database (NHIRD) from among 1 million individuals longitudinally observed from January 2000 through December 2011.
- Cases patients were defined as those hospitalized for aortic aneurysm or dissection.
- One hundred control patients were matched for each case based on age and sex.
- Current use was defined as a filled fluoroquinolone prescription within 60 days of the aortic aneurysm or dissection. Past use refers to a filled fluoroquinolone prescription between 61 and 365 days prior to the aortic aneurysm

JAMA Intern Med. 2015;175(11):1839-1847

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

Fluoroquinolone Use[a]	Effect Estimate, Rate Ratio (95% CI)	
	Matched on Age Group, Sex, and Year	Adjusted by Individual Confounders
Current	2.93 (2.17-3.97)[b]	2.28 (1.67-3.13)[b]
Past	1.82 (1.44-2.29)[b]	1.49 (1.18-1.90)[c]
Any use in prior year	2.11 (1.75-2.55)[b]	1.69 (1.39-2.06)[b]

Fluoroquinolone Use[a]	Effect Estimate, Rate Ratio (95% CI)	
	Propensity Score Adjusted	Propensity Score Matched
Current	2.43 (1.83-3.22)[b]	1.75 (1.11-2.74)[d]
Past	1.48 (1.18-1.86)[b]	1.19 (0.85-1.66)
Any use in prior year	1.74 (1.44-2.09)[b]	1.37 (1.04-1.79)[d]

JAMA Intern Med. 2015;175(11):1839-1847

Oral Fluoroquinolone and the Risk of Aortic Dissection

- A case crossover study takes into account the paired nature of the observations (within-subjects comparisons of exposure) so as to match out all intra individual time-invariant covariates, minimizing the risk of bias due to unmeasured confounding.

- Disease risk score (DRS)-matched case-time-control study to minimize the risk of time-trend bias associated with the case-only design

J Am Coll Cardiol 2018;72:1369–78

American Journal of Epidemiology

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The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events

- A case-control design involving only cases may be used when brief exposure causes a transient change in risk of a rare acute-onset disease.
- The design resembles a retrospective nonrandomized crossover study but differs in having only a sample of the base population-time.
- The duration of the effect period is assumed to be that which maximizes the rate ratio estimate. Self matching of cases eliminates the threat of control-selection bias and increases efficiency.

Am J Epidemiol 1991:133:144-53

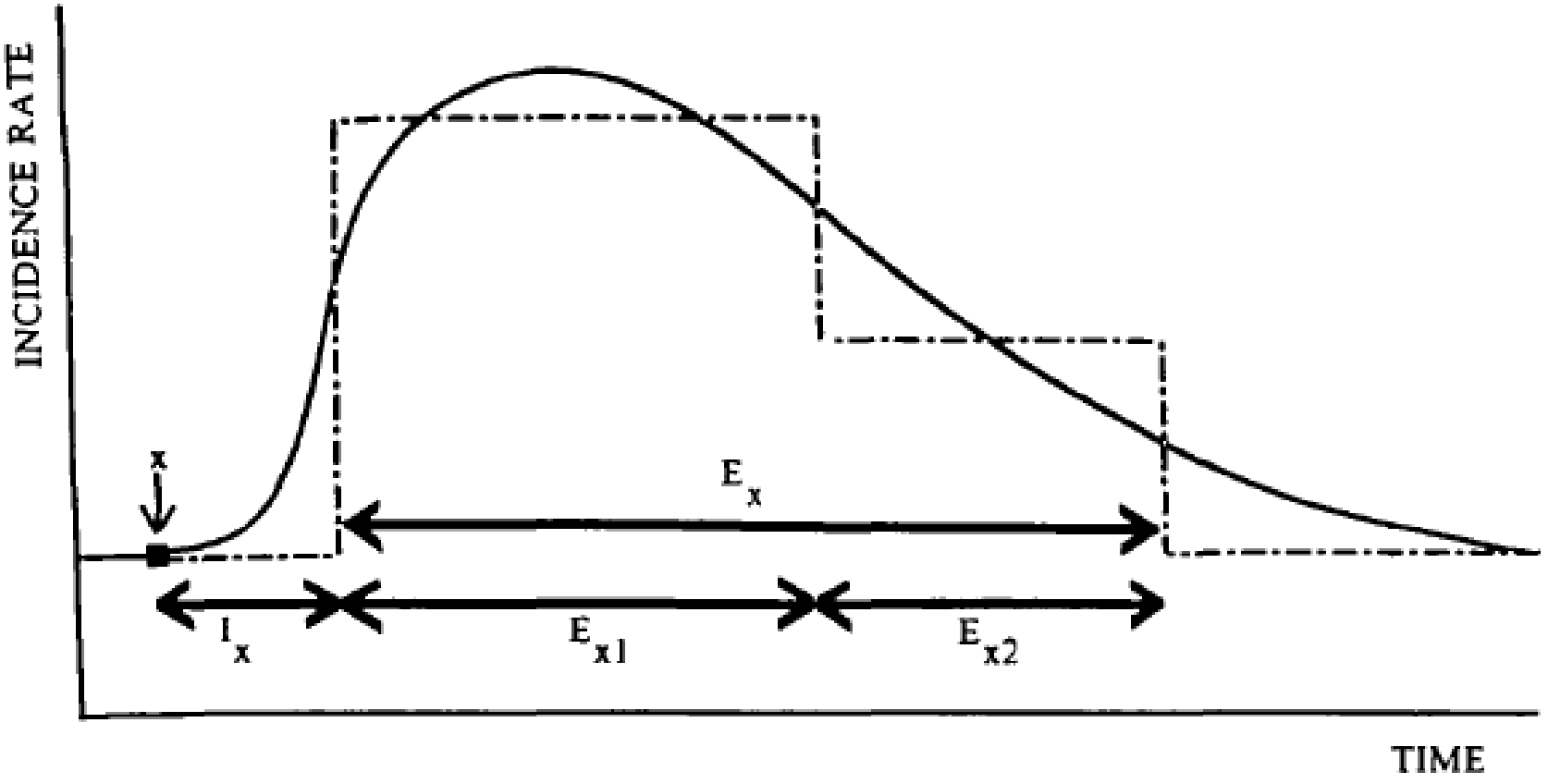


FIGURE 1. An epidemic curve (solid line) for acute-onset disease following a point exposure (x) with a transient effect. The step-function (dotted line) is a simplification of the curve showing an estimate of the population induction time (I_x) and the effect-period (E_x), comprising a high-risk effect-period (E_{x1}) and a moderate-risk effect-period (E_{x2}).

The Case-Time-Control Design

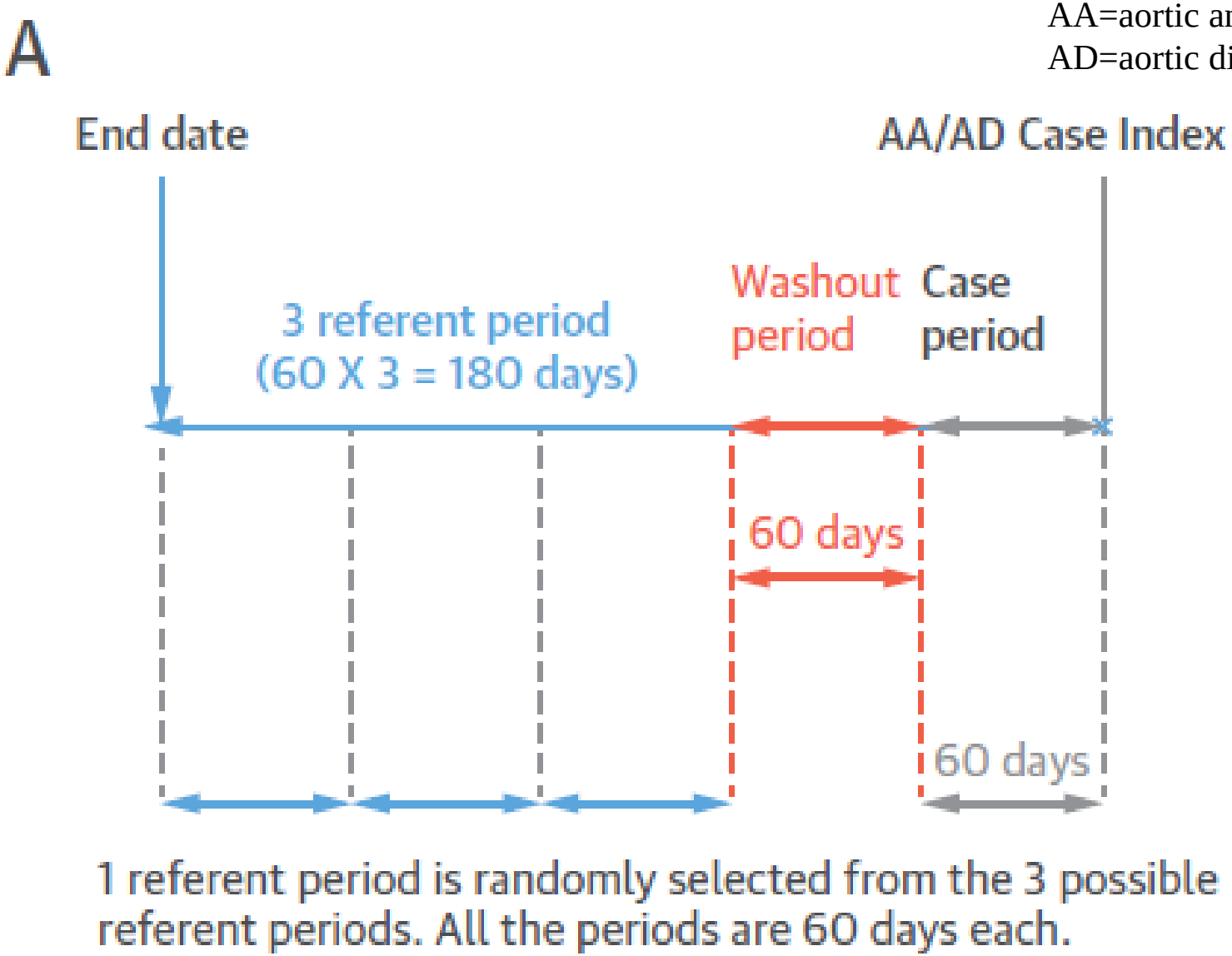
Samy Suissa

Assessing the known or intended effects of a drug using non-experimental epidemiologic designs is often infeasible because of the absence of accurate data on a major confounder, the severity of the disease treated by this drug. To circumvent this problem of confounding by indication, I propose the case-time-control design, which does not require a measure of this confounder. Instead, the design uses subjects from a conventional case-control design as their own controls and thus requires that exposure be measurable at two or more points in time. I present a logistic model to estimate relative risks under this design and illustrate the method with data from a case-control study of 129 cases of fatal or near-fatal asthma and 655 controls. The exposure of interest was quantity of use of inhaled beta-ago-

(Epidemiology 1995;6:248–253)

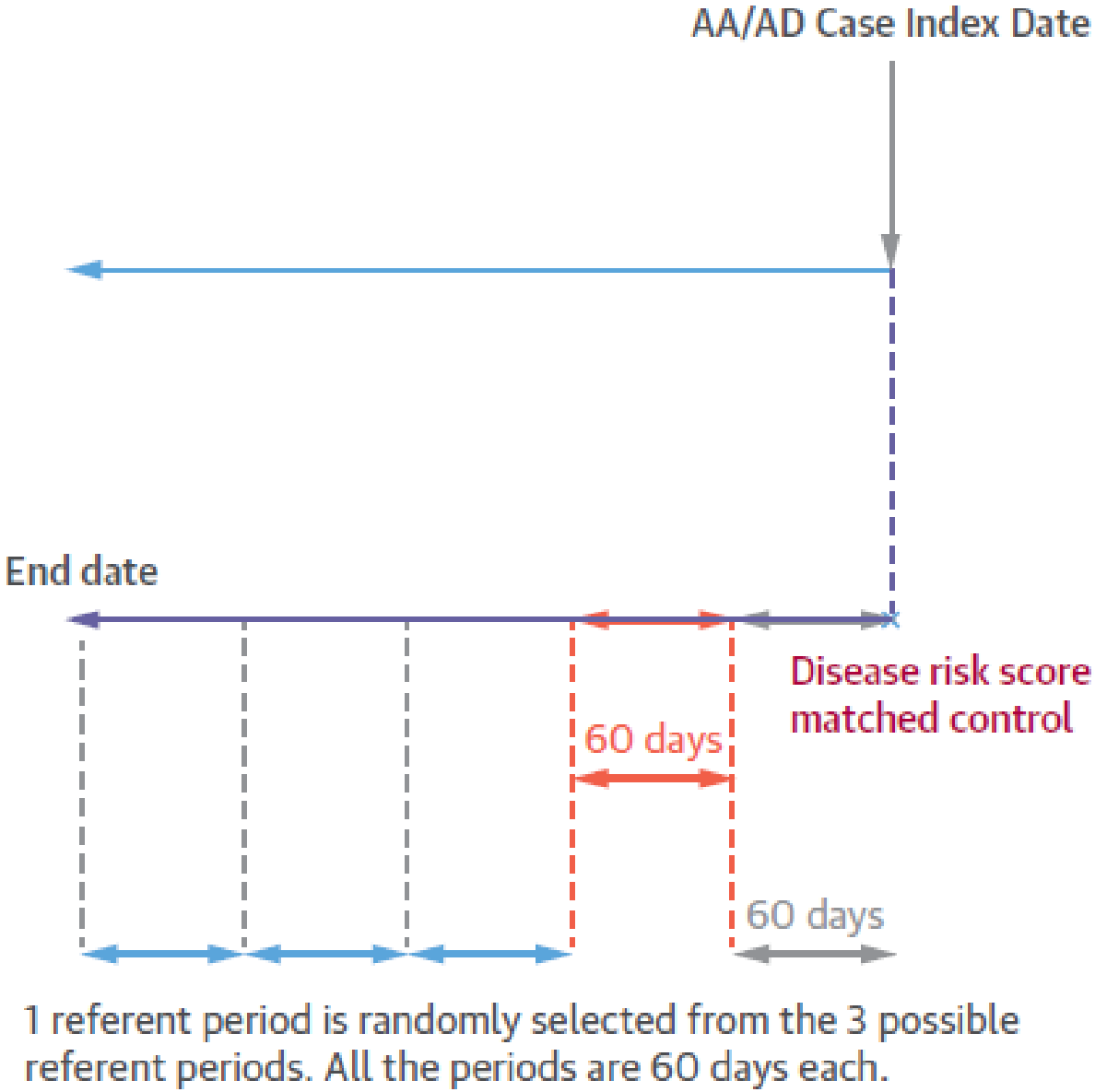
Case-crossover design

AA=aortic aneurysm
AD=aortic dissection



J Am Coll Cardiol 2018;72:1369–78

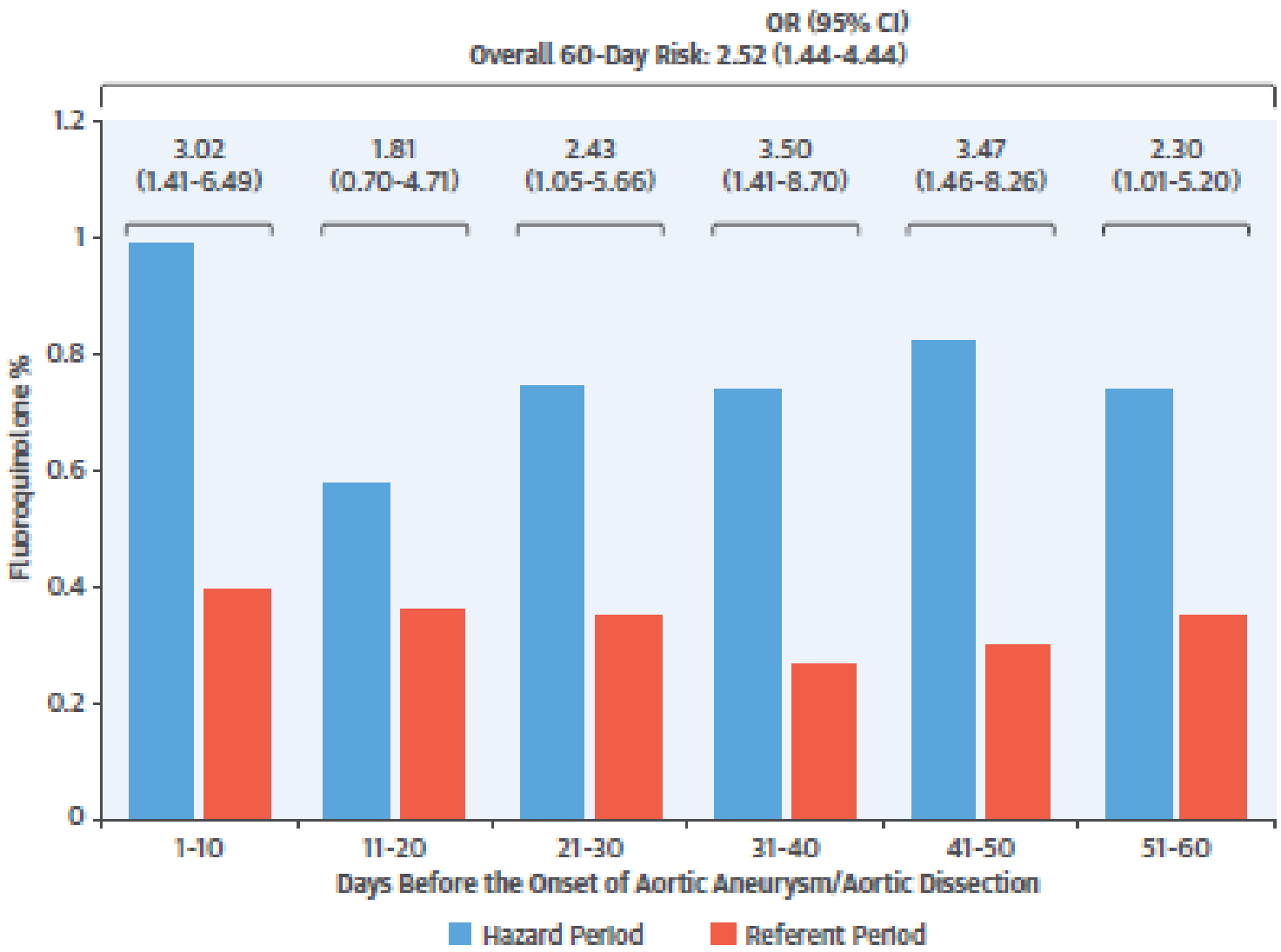
Disease risk score (DRS)-matched case-time-control study design



AA=aortic aneurysm
AD=aortic dissection

J Am Coll Cardiol 2018;72:1369–78

CENTRAL ILLUSTRATION Fluoroquinolones and the Risk of Aortic Aneurysm/Aortic Dissection Within 60 Days



Lee, C.-C. et al. J Am Coll Cardiol. 2018;72(12):1369-78.

CI = confidence interval; OR = odds ratio.

J Am Coll Cardiol 2018;72:1369–78

	Odds Ratio (95% CI)*
Case-crossover	2.71 (1.14–6.46)
Control-crossover	0.75 (0.32–1.78)
Case-time-control	3.61 (3.56–3.63)

TABLE 2 Main Analysis on the Estimates of the Relationship Between Exposure of Fluoroquinolone and AD or AAs

	Exposed Only in Hazard Period	Exposed Only in Referent Period	Exposed in Both Periods	Nonexposed in Both Periods	Odds Ratio (95% CI)*
Case-crossover	19	7	2	1,185	2.71 (1.14-6.46)
Control-crossover	9	12	2	1,190	0.75 (0.32-1.78)
Case-time-control	NA	NA	NA	NA	3.61 (3.56-3.63)

Values are n, unless otherwise indicated. *Calculated by McNemar's test: the ratio of subjects exposed only in the hazard period to subjects exposed in referent period.
AA = aortic dissection; AD = aortic aneurysm; CI = confidence interval; NA = not applicable.

J Am Coll Cardiol 2018;72:1369–78

TABLE 4 Duration-Response Analysis

Cumulative Fluoroquinolone Use	Exposed Individuals in Hazard Period (n = 1,213)	Exposed Individuals in Referent Period (n = 6,065)	Odds Ratio (95% CI)
<3 days	1,192 (98.27)	6,017 (99.21)	Reference group
3–14 days	14 (1.15)	32 (0.53)	2.41 (1.25–4.65)
>14 days	7 (0.58)	16 (0.26)	2.83 (1.06–7.57)

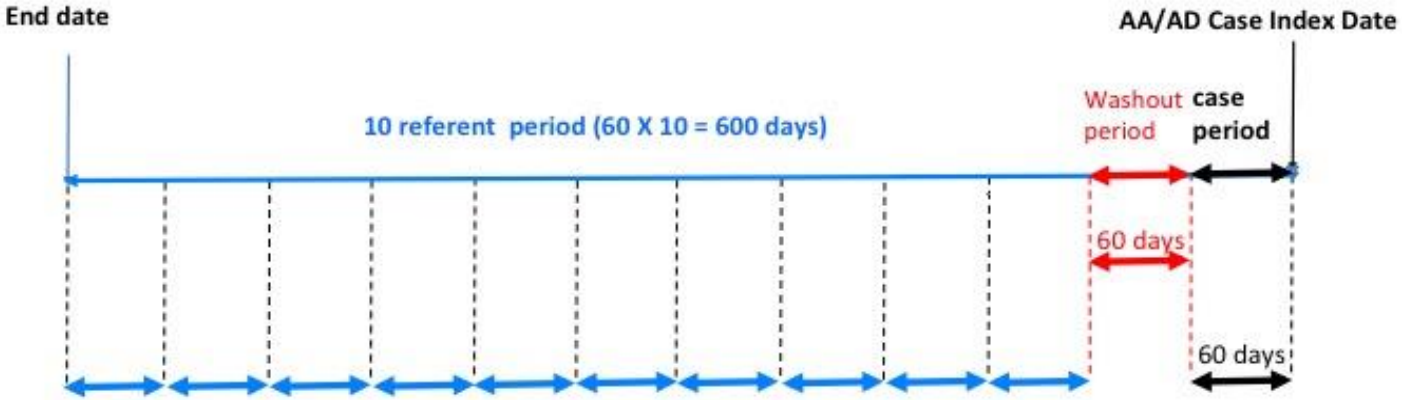
Values are n (%), unless otherwise indicated.

Abbreviations as in Table 2.

J Am Coll Cardiol 2018;72:1369–78

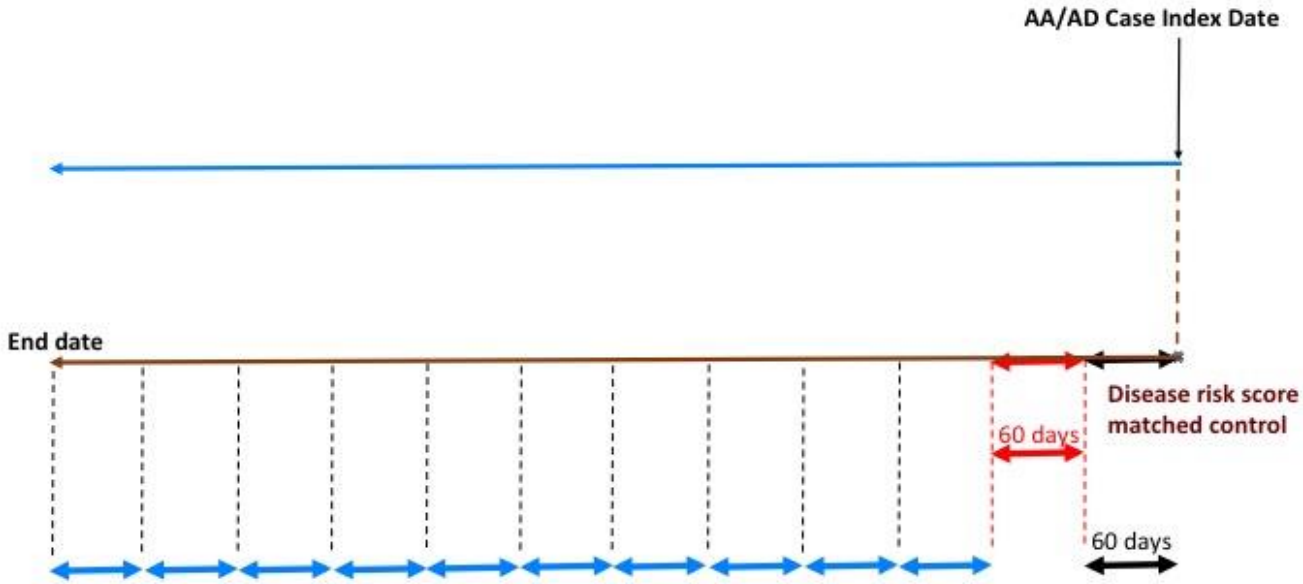
Thanks for your attention!

Mount Mayon, Bicol Region, The Philippines



5 referent periods are randomly selected
in the main analyses are 60days each.

AA stands for Aortic Aneurysm; AD stands for



5 referent periods are randomly selected from the 10 possible referent periods. All the periods in the main analyses are 60days each.

AA stands for Aortic Aneurysm; AD stands for Aortic Dissection

	Adjusted Odds Ratio (95% CI)*
Case-crossover	2.05 (1.13–3.71)
Control-crossover	0.83 (0.42–1.64)
Case-time-control	2.47 (2.26–2.69)

TABLE 3 Sensitivity Analysis Investigating Whether Time-Variant Confounders Might Affect the Risk of AA/AD by Using a 1:5 Ratio of Hazard Period to Referent Period

	Exposed Individuals in Hazard Period (n = 1,213)	Exposed Individuals in Referent Period (n = 6,065)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Case-crossover	21 (0.017)	48 (0.008)	2.52 (1.44-4.44)	2.05 (1.13-3.71)
Control-crossover	11 (0.009)	56 (0.0092)	0.98 (0.50-1.92)	0.83 (0.42-1.64)
Case-time-control	NA	NA	2.57 (2.31-2.88)	2.47 (2.26-2.69)

Values are n (%), unless otherwise indicated. *Calculated by multivariate conditional logistic regression with adjustment of time-varying confounders.
Abbreviations as in Table 2.

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Fluoroquinolones and collagen in the aortic wall

- Fluoroquinolones have chelating properties against several metal ions (e.g., calcium, magnesium, aluminum), which are essential for type 1 collagen synthesis.
- Fluoroquinolones can decrease collagen synthesis by increasing the expression of matrix metalloproteinases, which lead to extracellular matrix degradation and medial layer degeneration

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