

# Web appendix: Supplementary material

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

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**WebTable 1.** ICD-10 and ATC codes for exclusions

<b>Diagnosis</b>	<b>ICD-10 or ATC code</b>
Endstage illness (dementia, severe malnutrition, cachexia, coma, gangrene)	ICD-10: E105B, E115B, E40, E41, E42, E43, F00, F01, F02, F03, G30, I702A, R029, R402, R64, Z991 ATC: N06D
Drug/alcohol misuse	ICD-10: F10, F11, F12, F13, F14, F15, F16, F18, F19, R781, R782, R783, R784, R785, T40

**WebTable 2.** Covariates included in propensity Score with ICD-10 and ATC codes

<b>Covariate</b>	<b>Code</b>
<b>Demographic characteristics<sup>a</sup></b>	
Sex	
Age (continuous)	
Region of residence (6 categories)	
<b>Medical history<sup>b</sup></b>	
	<b>ICD-10 code</b>
Acute coronary syndrome	I200, I21-22
Other ischemic heart disease	I11 (not I110), I20 (not I200), I24, I25
Heart failure/cardiomyopathy	I110, I130, I132, I42, I43, I50, J81
Valve disorders	I34-37
Cerebrovascular disease	G45, G46, I60-69
Arterial disease	I65, I70, I72-I77, K550, K551
Arrhythmia	I44-49
Cardiac surgery/invasive cardiac procedure in previous yr	procedure code F
Lung disease	I27, J84, R092, E662, J40-47, J60-70, J92, J96, J982, J983; procedure code GGB
Cancer	C00-C43, C45-C97
Cancer in previous yr	C00-C43, C45-C97
Liver disease	B18, I850, I859, I982, K70-K77
Renal disease	I12, I13, N00-08, N17, N18, N19, N25, Z49
Rheumatic disease	M05-09, M30-34, M351, M353, M45
Psychiatric disorder	F04-09, F20-99
<b>Prescription-drug use in previous yr<sup>c</sup></b>	
	<b>ATC code</b>
ACE-inhibitor or ARB	C09A-D
Calcium channel blocker	C08C, C08D
Loop diuretic	C03C, C03EB
Other diuretic	C03A, C03B, C03D, C03EA
Beta-blocker	C07
Digoxin	C01AA05
Nitrates	C01DA
Platelet inhibitor	B01AC
Anticoagulant	B01AA
Lipid lowering drug	C10
Oral antidiabetic drug	A10B
Insulin	A10A
Antidepressant	N06A
Antipsychotic	N05A
Anxiolytic, hypnotic or sedative	N05B, N05C
Beta-2 agonist inhalant	R03AC
Anticholinergic inhalant	R03BB
Glucocorticoid inhalant	R03BA, R03AK
Oral glucocorticoid	H02AB
NSAID	M01A
Opiate	N02A
Systemic hormone replacement therapy	G03CA03, G03CA04, G03CA53, G03CA57, G03FA01, G03FA11, G03FA12, G03FA15, G03FA17, G03FB01, G03FB05, G03FB06, G03FB09, G03FB11, G03HB01, G03XC01, G03DC05, G03CX01
No. of drugs used (1-2, 3-5, 6-9, ≥10)	
<b>Non-study antibiotic in previous 120 d<sup>c</sup></b>	J01 (not J01MA, not J01CA04)
<b>Health care utilization<sup>b</sup></b>	
Hospitalization due to cardiovascular	

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causes in previous yr
Hospitalization due to non-cardiovascular causes in previous yr
Outpatient contact due to cardiovascular causes in previous yr
Outpatient contact due to non-cardiovascular causes in previous yr
Emergency department visit in previous 30 d

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<sup>a</sup>Data from Statistics Sweden (the national bureau of statistics)

<sup>b</sup>Data from National Patient Register

<sup>c</sup>Data from National Prescribed Drug Register

ACE angiotensin-converting enzyme; ARB angiotensin receptor blocker; NSAID nonsteroidal antiinflammatory drug; SD standard deviation

**WebTable 3.** ICD-10 codes for primary outcome

<b>Primary outcome</b>	<b>Data sources</b>	<b>Outcome capture</b>	<b>ICD-10 code</b>
Aortic aneurysm or dissection (any)	National Patient Register and Cause of Death Register	Admission to hospital or emergency department, or underlying cause of death	I71.0-I71.9 Includes: I71.0 Dissection of aorta I71.1 Thoracic aortic aneurysm, ruptured I71.2 Thoracic aortic aneurysm, without rupture I71.3 Abdominal aortic aneurysm, ruptured I71.4 Abdominal aortic aneurysm, without rupture I71.5 Thoracoabdominal aortic aneurysm, ruptured I71.6 Thoracoabdominal aortic aneurysm, without rupture I71.8 Aortic aneurysm of unspecified site, ruptured I71.9 Aortic aneurysm of unspecified site, without rupture

**WebTable 4.** ICD-10 codes for outcome definition in sensitivity analyses

<b>Analysis</b>	<b>Data sources</b>	<b>Outcome capture</b>	<b>ICD-10 code</b>
Cases of aortic aneurysm with dissection or rupture alone, either associated with admission to hospital or emergency department or that were the underlying cause of death	National Patient Register and Cause of Death Register	Admission to hospital or emergency department, or underlying cause of death	I71.0, I71.1, I71.3, I71.5, I71.8
Cases of aortic aneurysm associated with admission to hospital alone (not emergency department) or that were the underlying cause of death	National Patient Register and Cause of Death Register	Admission to hospital or underlying cause of death	I71.0-I71.9
Cases of aortic aneurysm that also had aortic surgery within 30 days of the date of diagnosis, or that were the underlying cause of death	National Patient Register and Cause of Death Register	Admission to hospital or underlying cause of death	I71.0-I71.9 + procedure code: FCA (not FCA83, FCA84), FCB (not FCB80, FCB82), FCC (not FCC80, FCC82), FCD (not FCD80, FCD82), FCE00, FCW96, PCG10, PCQ10, PDG (not PDG30), PDH (not PDH30), PDN10, PDP10, PDQ10, PDQ21

**WebTable 5.** Baseline characteristics before propensity score matching

<b>Characteristic</b>	<b>Oral fluoroquinolones (N=560,768)</b>	<b>Amoxicillin (n=440,504)</b>	<b>Standardized difference (%)</b>
<i>No of persons</i>	404,545	320,021	<i>N.A.</i>
Male sex, no. (%)	311,549 (56)	180,208 (41)	29.6
Age, yr, mean (SD)	69.4 (11.1)	67.7 (10.4)	15.2
Region of residence, no. (%)			
Stockholm metropolitan area	114,494 (20)	123,372 (28)	17.8
Rest of Mid Sweden	116,456 (21)	77,247 (18)	8.2
Southern Sweden metropolitan areas	94,595 (17)	70,772 (16)	2.2
Rest of Southern Sweden	182,431 (33)	135,236 (31)	3.9
Northern Sweden	52,103 (9)	33,394 (8)	6.2
Missing	689 (0.1)	483 (0.1)	0.4
Medical history, no. (%)			
Acute coronary syndrome	21,631 (4)	17,210 (4)	0.3
Other ischemic heart disease	57,942 (10)	50,142 (11)	3.4
Heart failure/cardiomyopathy	27,899 (5)	28,646 (7)	6.6
Valve disorders	10,089 (2)	30,428 (7)	25.2
Cerebrovascular disease	37,609 (7)	24,690 (6)	4.6
Arterial disease	15,025 (3)	11,396 (3)	0.6
Arrhythmia	56,305 (10)	52,657 (12)	6.1
Cardiac surgery/invasive cardiac procedure in previous yr	23,864 (4)	30,752 (7)	11.9
Lung disease	39,656 (7)	59,669 (14)	21.4
Cancer	72,326 (13)	44,044 (10)	9.1
Cancer in previous yr	48,395 (9)	26,847 (6)	9.7
Liver disease	5221 (1)	4867 (1)	1.7
Renal disease	14,811 (3)	12,339 (3)	1.0
Rheumatic disease	21,271 (4)	23,434 (5)	7.3
Psychiatric disorder	33,633 (6)	27,711 (6)	1.2
Prescription-drug use in previous yr, no. (%)			
ACE-inhibitor or ARB	182,479 (33)	148,426 (34)	2.5
Calcium channel blocker	99,737 (18)	80,260 (18)	1.1
Loop diuretic	78,508 (14)	67,566 (15)	3.8
Other diuretic	79,142 (14)	66,897 (15)	3.0
Beta-blocker	177,092 (32)	147,105 (33)	3.9
Digoxin	13,555 (2)	12,497 (3)	2.6
Nitrates	51,974 (9)	40,423 (9)	0.3
Platelet inhibitor	158,160 (28)	114,984 (26)	4.7
Anticoagulant	33,918 (6)	43,539 (10)	14.2
Lipid lowering drug	150,160 (27)	128,689 (29)	5.4
Oral antidiabetic drug	52,582 (9)	36,130 (8)	4.2
Insulin	32,443 (6)	22,997 (5)	2.5
Antidepressant	92,578 (17)	75,391 (17)	1.6
Antipsychotic	15,082 (3)	9311 (2)	3.8
Anxiolytic, hypnotic or sedative	173,213 (31)	135,935 (31)	0.1
Beta-2 agonist inhalant	48,649 (9)	70,154 (16)	22.2
Anticholinergic inhalant	21,310 (4)	38,760 (9)	20.7
Glucocorticoid inhalant	64,393 (12)	90,660 (21)	25.0
Oral glucocorticoid	71,900 (13)	79,409 (18)	14.4
NSAID	163,654 (29)	124,384 (28)	2.1
Opiate	118,780 (21)	96,053 (22)	1.5
Systemic hormone replacement therapy	91,772 (16)	75,893 (17)	2.3
No. of drugs used			

1-2	124,062 (22)	88,054 (20)	2.1
3-5	177,064 (32)	137,075 (31)	1.5
6-9	159,914 (29)	132,612 (30)	2.3
≥10	99,728 (18)	82,763 (19)	2.1
Non-study antibiotic in previous 120 d, no. (%)	186,866 (33)	111,748 (25)	17.5
Health care utilization, no. (%)			
Hospitalization due to cardiovascular causes in previous yr	25,576 (5)	22,926 (5)	3.0
Hospitalization due to non-cardiovascular causes in previous yr	176,447 (32)	127,760 (29)	5.4
Outpatient contact due to cardiovascular causes in previous yr	39,143 (7)	42,753 (10)	9.9
Outpatient contact due to non-cardiovascular causes in previous yr	305,580 (55)	236,452 (54)	1.6
Emergency department visit in previous 30 d	40,357 (7)	19,218 (4)	12.2



**WebTable 6.** Cases of aortic aneurysm or dissection occurring in 60-day risk period from start of treatment with oral fluoroquinolones, as compared with amoxicillin, according to type of aneurysm

<b>Type of Aneurysm (ICD-10 code)</b>	<b>Fluoroquinolones</b>	<b>Amoxicillin</b>	<b>Hazard Ratio (95% CI)</b>
	<i>No. of Cases</i>	<i>No. of Cases</i>	
Dissection of aorta (I710)	9	10	0.93 (0.38-2.29)
Thoracic or thoracoabdominal aortic aneurysm (I711, I712, I715, I716)	15	11	1.90 (1.22-2.96)
Abdominal aortic aneurysm (I713, I714)	36	14	
Aortic aneurysm of unspecified site (I718, I719)	4	5	