

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix:

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Sources of data

Information on use of azithromycin (anatomical chemical classification [ATC] code J01FA10) and penicillin V (J01CE02) was obtained from the National Prescription Registry.¹ This nationwide registry has records on all prescriptions filled at pharmacies in Denmark since 1995, including the date of filling the prescription and the ATC code. Information on causes of death was obtained from the Danish Register of Causes of Death,² which, based on information on death certificates, records all causes of death in Denmark, classified according to international classification of diseases (ICD). ICD-10 codes used to define study outcomes are shown Table S2. This register is close to complete; each year only 0.3 to 0.6% of all deaths are not fully reported.² Although validation studies of all cardiovascular causes of death have not been performed, based on 1794 cases in the Register of Causes of Death with myocardial infarction recorded as the underlying cause of death, 97.2% were classified as definite or possible myocardial infarction following extensive review of medical records.³ The sensitivity for definitive myocardial infarction was 89%.³ Information on potential confounders (Table S1) was obtained from the Civil Registration System (the main administrative register in Denmark),⁴ the National Prescription Registry,¹ and the National Patient Register.⁵ The National Patient Register holds individual-level information on outpatient and emergency department visits and inpatient admissions to all hospitals in Denmark; physician-assigned diagnoses are coded according to ICD-10.⁵ The National Patient Register has demonstrated high validity in the identification of a wide range of serious diseases; the overall positive predicted value for the 19 conditions included in the Charlson Comorbidity Index was estimated to 98%.⁶

Selection of Control Episodes of No Use of Antibiotics

To create a pool of potential controls for matching, each azithromycin episode was randomly assigned up to 10 control episodes, starting on the index date in persons with the same sex and birth date, who were not using azithromycin on the index date. The selected controls episodes were all unique and non-overlapping in time. Control episodes that did not fulfill the inclusion criteria were excluded. With this approach, a total of 11,024,100 potential control episodes of no use of antibiotics were selected. Following propensity score estimation, episodes of use of azithromycin were propensity score-matched 1:1 to control episodes of no use of antibiotics, using greedy 5->1 digit matching technique.⁷ Propensity scores methods represent a useful approach to reduce confounding, allowing a large number of covariates to be combined into a single score, representing the participant's likelihood of exposure.⁸ Matching on levels of the propensity score removes participants with no comparable controls and should produce a cohort that is on average balanced on all measured covariates.⁹ The propensity score was estimated using logistic regression, including as predictors all variables listed in Table S1.

Estimated Adjusted Absolute Risk Difference per 1,000,000 Treatment Episodes with Use of Azithromycin as Compared with Penicillin V.

We estimated the adjusted absolute risk difference per 1,000,000 treatment episodes with current use of azithromycin as compared with penicillin V. The risk difference associated with azithromycin was calculated as $(RR_a - 1) \cdot I_0$, as outlined by Ray et al.¹⁰ In this notation, RR_a corresponds to the estimated RR for azithromycin versus penicillin V and I_0 corresponds to the IR per 1,000,000 treatment episodes with use of penicillin V. Based on the confidence interval for the RR, we also estimated lower and upper 95% confidence limits for the absolute risk difference. Details of the calculations follow below.

IR per person-year with use of penicillin =

146 cardiovascular deaths/99,250 person-years of follow-up = 0.0014710327

Time of follow-up per 1,000,000 treatment episodes =

5,000,000 person-days \approx 13,689 person-years

I_0 = IR per 1,000,000 treatment episodes with use of penicillin V =

$13,689 \times 0.0014710327 \approx 20.1$

Given the adjusted RR of 0.93 for use of azithromycin as compared with penicillin V, the absolute risk difference per 1,000,000 treatment episodes was calculated as:

$(RR_a - 1) \cdot I_0 = (0.93 - 1) \times 20.1 = -1.407$.

From the 95% confidence limits, the lower bound was analogously calculated as

$(0.56 - 1) \times 20.1 = -8.844$

and the upper bound as

$(1.55 - 1) \times 20.1 = 11.055$.

Thus, after rounding, the excess number of cardiovascular deaths per 1,000,000 treatment episodes azithromycin as compared with penicillin V was estimated to -1 (95% CI -9 to 11).

Table S1. Covariates Included in Propensity Score With ICD and ATC Codes.

Covariate	Codes
Demographic characteristics^a	
Sex	
Age (5-year intervals)	
Country of birth (Denmark, Europe, Other)	
Region of residence (5 categories)	
Degree of urbanization (6 categories)	
Calendar year (2-year intervals)	
Season (4 categories)	
Medical history^b	
	ICD codes
Acute coronary syndrome	ICD-8: 410-411; ICD-10: I200, I21-22
Other ischemic heart disease	ICD-8: 412-414; ICD-10: I11 (not I110), I20 (not I200), I24, I25
Heart failure/cardiomyopathy	ICD-8: 402, 404, 425, 42709-42719, 428; ICD-10: I110, I130, I132, I42, I43, I50, J81
Valve disorders	ICD-8: 394-397, 424; ICD-10: I34-37
Cardiac surgery/invasive cardiac procedure in past year	procedure code KF
Congenital heart disease	ICD-8: 746, 74709, 74719, 74729, 74739; ICD-10: Q20-26
Cerebrovascular disease	ICD-8: 430-438; ICD-10: G45-46, I60-69
Arterial disease	ICD-8: 432, 440-442, 444-445, 447; ICD-10: I65, I70-I77, K550-551
Arrhythmia	ICD-8: 42720-42797; ICD-10: I44-49
Venous thromboembolism	ICD-8: 450-452; ICD-10: I26, I801-809, I81
Renal disease	ICD-8: 403-404, 792, 580-584, 59309-59329; ICD-10: I12-13, N00-08, N17-19, N25, Z49, Z940, Z992
Liver disease	ICD-8: 45600, 45601, 45609, 570-573; ICD-10: B18, I850, I859, I982, K70-K77
Chronic lung disease	ICD-8: 426, 490-493, 515-519; ICD-10: I27, J40-47, J60-70, J84, J92, J96, J982, J983
Serious neurologic disease	ICD-8: 340-341, 330-332, 344, 348; ICD-10: G10-14, G35-37, G71, G82
Rheumatic disease	ICD-8: 446, 56904, 712, 715-716, 734; ICD-10: M05-09, M30-34, M351, M353, M45
Cancer (does not include non-melanoma skin cancer)	ICD-8: 140-172, 174-207; ICD-10: C00-C43, C45-C97
Other endstage illness (malnutrition, coma, gangrene)	ICD-8: 267-268, 445, 78009; ICD-10: E40-E43, R64, R402, I702A, E105B, E115B, R029
Alcohol-/drug abuse	
Dementia	ICD-8: 290, 293, 794; ICD-10: F00-F03, G30
Hospital contact for injury/poisoning in past year	ICD-8: n.a.; ICD-10: S00-T98
Prescription drugs used in past year^c	
	ATC codes
ARB/ACE-I	C09A-D
Calcium channel blockers	C08C-D
Loop diuretics	C03C, C03EB
Other diuretics	C03A, C03B, C03D, C03EA
Beta-blockers	C07
Anti-arrhythmics class I and III	C01B
Digoxin	C01AA05
Nitrates	C01DA
Platelet inhibitors	B01AC
Anticoagulants	B01AA
Lipid lowering drugs	C10
Oral antidiabetic drugs	A10B
Insulin	A10A
Antidepressants	N06A
Antipsychotics	N05A
Anxiolytics, hypnotics and sedatives	N05B, N05C
Beta-2 agonist inhalants	R03AC
Corticosteroid inhalants	R03BA, R03AK
Xantines	R03DA
Anticholinergic inhalants	R03BB
Oral corticosteroids	H02AB
NSAIDs	M01A
Opiates	N02A
Drugs for alcohol/opiate dependence	N07BB-BC
Antiepileptics	N03

Dopaminergic antiparkinson drugs	N04B
Systemic hormone replacement therapy	G03CA03, G03CA04, G03CA53, G03CA57, G03FA01, G03FA11, G03FA12, G03FA15, G03FA17, G03FB01, G03FB05, G03FB06, G03FB09, G03FB11, G03HB01, G03XC01, G03DC05, G03CX0
Number of drugs used (1-2; 3-5; 6-9; ≥ 10)	
Health care use^b	
Number of cardiovascular emergency visits/ hospitalizations in past year (0; 1; ≥ 2)	
Number of other emergency visits/ hospitalizations in past year (0; 1; ≥ 2)	
Cardiovascular outpatient hospital contacts in past year (0; 1; ≥ 2)	
Other outpatient hospital contacts in past year (0; 1; ≥ 2)	
Emergency visit in past 7 days (yes/no)	
Emergency visit in past 30 days (yes/no)	

ATC, anatomic therapeutic chemical; ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor; ICD, international classification of diseases; NSAID, non-steroidal anti-inflammatory drug.

^a Data from Central Person Register.

^b Data from National Patient Register.

^c Data from National Prescription Register.

Table S2. ICD Codes for Study Outcomes as Identified from The Danish Cause of Death Register.

Cause of death	ICD-10 codes
Cardiovascular	I00-99, R960, R961
Cardiac	I11, I13, I20-25, I27, I30-52
Non-cardiovascular	All other

ICD, international classification of diseases.

Table S3. Baseline Characteristics of Individuals Using Azithromycin and Included in Analyses vs. Non-Users of Antibiotics and vs. Users of Penicillin V, Denmark, 1997-2010.

This table shows the distribution of all 61 variables included in the propensity score (Table 1 in main manuscript shows selected characteristics)

	Cohort of azithromycin users and non-users matched according to propensity score		Cohort of azithromycin users and penicillin V users (unmatched)	
	Azithromycin (N = 1,102,050)	No antibiotic (N = 1,102,050)	Azithromycin (N = 1,102,419)	Penicillin V (N = 7,364,292)
Demographic characteristics				
Male sex	383,973 (34.8)	390,485 (35.4)	384,279 (34.9)	2,822,420 (38.3)
Age, mean (SD)	39.7 (13.9)	39.5 (13.8)	39.7 (13.9)	42.0 (12.8)
Country of birth				
Denmark	1,017,804 (92)	1,018,223 (92)	1,018,155 (92)	6,741,017 (92)
Europe	27,906 (3)	27,650 (3)	27,919 (3)	168,489 (2)
Other	56,340 (5)	56,177 (5)	56,345 (5)	454,786 (6)
Region of residence				
Greater Copenhagen	423,792 (38)	425,803 (39)	424,019 (38)	2,185,229 (30)
Zealand	168,370 (15)	168,926 (15)	168,414 (15)	1,241,137 (17)
Southern Denmark	221,494 (20)	221,193 (20)	221,543 (20)	1,690,249 (23)
Central Denmark	176,229 (16)	173,816 (16)	176,241 (16)	1,473,295 (20)
North Denmark	112,165 (10)	112,312 (10)	112,202 (10)	774,382 (11)
Degree of urbanization, population density/km ²				
≤ 49 inhabitants	55,837 (5)	55,388 (5)	55,852 (5)	467,039 (6)
50-99 inhabitants	249,355 (23)	248,206 (23)	249,388 (23)	2,075,225 (28)
100-199 inhabitants	223,820 (20)	223,039 (20)	223,878 (20)	1,669,358 (23)
≥ 200 inhabitants	105,921 (10)	106,037 (10)	105,946 (10)	656,440 (9)
Residence in Copenhagen suburbs	291,258 (26)	294,072 (27)	291,374 (26)	1,724,632 (23)
Residence in Copenhagen	175,859 (16)	175,308 (16)	175,981 (16)	771,598 (10)
Calendar year				
1997-1998	130,756 (12)	131,138 (12)	130,793 (12)	1,071,437 (15)
1999-2000	178,903 (16)	178,510 (16)	178,947 (16)	1,024,345 (14)
2001-2002	166,203 (15)	165,925 (15)	166,258 (15)	1,063,595 (14)
2003-2004	144,709 (13)	144,654 (13)	144,786 (13)	1,056,566 (14)
2005-2006	145,392 (13)	145,827 (13)	145,447 (13)	1,064,812 (14)
2007-2008	169,726 (15)	169,882 (15)	169,784 (15)	1,079,421 (15)
2009-2010	166,361 (15)	166,114 (15)	166,404 (15)	1,004,116 (14)
Season				
March-May	272,322 (25)	271,639 (25)	272,424 (25)	1,885,282 (26)
June-August	210,277 (19)	209,879 (19)	210,349 (19)	1,558,724 (21)
September-November	283,249 (26)	283,109 (26)	283,341 (26)	1,764,950 (24)
December-February	336,202 (31)	337,423 (31)	336,305 (31)	2,155,336 (29)
Medical history				
Acute coronary syndrome	13,850 (1)	13,686 (1)	13,860 (1)	114,441 (2)
Other ischemic heart disease	29,316 (3)	29,052 (3)	29,358 (3)	226,568 (3)
Heart failure/cardiomyopathy	7,384 (1)	7,301 (1)	7,388 (1)	56,850 (1)
Valve disorders	3,055 (<1)	2,995 (<1)	3,056 (<1)	28,313 (<1)
Cardiac surgery/invasive cardiac procedure in past year	1,556 (<1)	1,623 (<1)	1,556 (<1)	14,241 (<1)
Congenital heart disease	5,051 (<1)	5,112 (<1)	5,053 (<1)	33,328 (<1)
Cerebrovascular disease	14,098 (1)	13,837 (1)	14,098 (1)	116,359 (2)
Arterial disease	11,392 (1)	11,219 (1)	11,397 (1)	92,165 (1)
Arrhythmia	22,657 (2)	22,366 (2)	22,688 (2)	158,098 (2)
Venous thromboembolism	12,098 (1)	11,997 (1)	12,111 (1)	92,956 (1)
Renal disease	6,852 (1)	6,835 (1)	6,854 (1)	52,035 (1)
Liver disease	11,295 (1)	11,342 (1)	11,315 (1)	93,076 (1)
Chronic lung disease	90,675 (8)	88,131 (8)	90,980 (8)	464,349 (6)
Serious neurologic disease	7,869 (1)	7,938 (1)	7,872 (1)	62,058 (1)
Rheumatic disease	20,088 (2)	20,236 (2)	20,106 (2)	127,762 (2)
Cancer	31,836 (3)	31,566 (3)	31,859 (3)	224,943 (3)
Other endstage illness	2,862 (<1)	2,886 (<1)	2,865 (<1)	16,555 (<1)
Alcohol/drug abuse	38,552 (3)	38,877 (4)	38,588 (4)	301,709 (4)

Dementia	1,043 (<1)	1,026 (<1)	1,043 (<1)	9,630 (<1)
Hospital contact for injury/poisoning in past year	153,148 (14)	154,722 (14)	153,269 (14)	1,000,895 (14)
Prescription drugs used in past year				
ARB/ACE-I	65,581 (6)	64,241 (6)	65,598 (6)	497,673 (7)
Calcium channel blockers	36,888 (3)	36,184 (3)	36,896 (3)	292,871 (4)
Loop diuretics	26,280 (2)	25,707 (2)	26,308 (2)	187,579 (3)
Other diuretics	64,471 (6)	63,387 (6)	64,502 (6)	472,066 (6)
Beta-blockers	51,250 (5)	50,468 (5)	51,255 (5)	403,018 (5)
Anti-arrhythmics class I and III	1,265 (<1)	1,249 (<1)	1,266 (<1)	9,631 (<1)
Digoxin	2,926 (<1)	2,912 (<1)	2,929 (<1)	24,542 (<1)
Nitrates	9,159 (1)	9,128 (1)	9,165 (1)	71,464 (1)
Platelet inhibitors	36,719 (3)	36,106 (3)	36,732 (3)	301,629 (4)
Anticoagulants	6,089 (1)	6,064 (1)	6,089 (1)	58,719 (1)
Lipid lowering drugs	44,906 (4)	44,399 (4)	44,913 (4)	357,209 (5)
Oral antidiabetic drugs	15,956 (1)	15,993 (1)	15,959 (1)	149,626 (2)
Insulin	12,015 (1)	12,009 (1)	12,018 (1)	107,568 (1)
Antidepressants	110,479 (10)	109,915 (10)	110,539 (10)	758,977 (10)
Antipsychotics	24,925 (2)	24,819 (2)	24,927 (2)	223,728 (3)
Anxiolytics, hypnotics and sedatives	153,466 (14)	151,403 (14)	153,609 (14)	1,000,456 (14)
Beta-2 agonist inhalants	117,649 (11)	114,677 (10)	117,976 (11)	624,493 (8)
Corticosteroid inhalants	109,120 (10)	105,068 (10)	109,452 (10)	536,086 (7)
Xantines	6,263 (1)	5,731 (1)	6,343 (1)	29,333 (<1)
Anticholinergic inhalants	10,702 (1)	9,411 (1)	10,900 (1)	43,203 (1)
Oral corticosteroids	72,937 (7)	70,481 (6)	73,158 (7)	388,631 (5)
NSAIDs	290,125 (26)	289,116 (26)	290,236 (26)	2,146,477 (29)
Opiates	96,731 (9)	96,204 (9)	96,805 (9)	721,682 (10)
Drugs for alcohol/opiate dependence	10,202 (1)	10,037 (1)	10,205 (1)	105,930 (1)
Antiepileptics	21,759 (2)	21,527 (2)	21,763 (2)	181,793 (2)
Dopaminergic antiparkinson drugs	2,574 (<1)	2,587 (<1)	2,574 (<1)	21,394 (<1)
Systemic hormone replacement therapy	98,050 (9)	96,798 (9)	98,082 (9)	529,113 (7)
Number of drugs used				
1-2	386,451 (35)	384,078 (35)	386,451 (35)	2,927,365 (40)
3-5	382,923 (35)	390,211 (35)	382,923 (35)	2,572,583 (35)
6-9	211,575 (19)	212,851 (19)	211,576 (19)	1,257,287 (17)
≥ 10	121,101 (11)	114,910 (10)	121,469 (11)	607,057 (8)
Health care use				
Cardiovascular emergency visits/hospitalizations in past year				
0	1,085,029 (98)	1,085,103 (98)	1,085,391 (98)	7,227,975 (98)
1	8,311 (1)	8,212 (1)	8,315 (1)	64,962 (1)
≥ 2	8,710 (1)	8,735 (1)	8,713 (1)	71,355 (1)
Other emergency visits/hospitalizations in past year				
0	833,946 (76)	833,789 (76)	834,121 (76)	5,504,124 (75)
1	91,850 (8)	92,306 (8)	91,912 (8)	590,498 (8)
≥ 2	176,254 (16)	175,955 (16)	176,386 (16)	1,269,670 (17)
Cardiovascular outpatient hospital contacts in past year				
0	1,079,787 (98)	1,080,012 (98)	1,080,144 (98)	7,189,179 (98)
1	9,648 (1)	9,605 (1)	9,653 (1)	72,701 (1)
≥ 2	12,615 (1)	12,433 (1)	12,622 (1)	102,412 (1)
Other outpatient hospital contacts in past year				
0	771,292 (70)	773,354 (70)	771,450 (70)	5,050,097 (69)
1	68,461 (6)	68,339 (6)	68,497 (6)	469,974 (6)
≥ 2	262,297 (24)	260,357 (24)	262,472 (24)	1,844,221 (25)
Emergency visit in past 7 days	4,665 (<1)	4,637 (<1)	4,677 (<1)	98,519 (1)
Emergency visit in past 30 days	16,191 (1)	16,306 (1)	16,210 (1)	172,786 (2)

ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

Table S4. Baseline Characteristics of Azithromycin and Penicillin V Users, Matched 1:1 According to Propensity Score.

	Azithromycin (N = 1,102,419)	Penicillin V (N = 1,102,419)
Demographic characteristics		
Male sex	384,279 (35)	384,588 (35)
Age, mean (SD)	39.7 (13.9)	39.7 (13.8)
Country of birth		
Denmark	1,018,155 (92)	1,018,211 (92)
Europe	27,919 (3)	27,896 (3)
Other	56,345 (5)	56,312 (5)
Region of residence		
Greater Copenhagen	424,019 (38)	424,851 (39)
Zealand	168,414 (15)	167,896 (15)
Southern Denmark	221,543 (20)	220,876 (20)
Central Denmark	176,241 (16)	176,195 (16)
North Denmark	112,202 (10)	112,601 (10)
Degree of urbanization, population density/km ²		
≤ 49 inhabitants	55,852 (5)	55,227 (5)
50-99 inhabitants	249,388 (23)	247,267 (22)
100-199 inhabitants	223,878 (20)	223,899 (20)
≥ 200 inhabitants	105,946 (10)	107,991 (10)
Residence in Copenhagen suburbs	291,374 (26)	292,418 (27)
Residence in Copenhagen	175,981 (16)	175,617 (16)
Calendar year		
1997-1998	130,793 (12)	129,726 (12)
1999-2000	178,947 (16)	177,748 (16)
2001-2002	166,258 (15)	166,194 (15)
2003-2004	144,786 (13)	144,805 (13)
2005-2006	145,447 (13)	145,802 (13)
2007-2008	169,784 (15)	170,711 (15)
2009-2010	166,404 (15)	167,433 (15)
Season		
March-May	272,424 (25)	272,063 (25)
June-August	210,349 (19)	210,411 (19)
September-November	283,341 (26)	285,176 (26)
December-February	336,305 (31)	334,769 (30)
Medical history		
Acute coronary syndrome	13,860 (1)	13,740 (1)
Other ischemic heart disease	29,358 (3)	29,294 (3)
Heart failure/cardiomyopathy	7,388 (1)	7,463 (1)
Valve disorders	3,056 (<1)	2,957 (<1)
Cardiac surgery/invasive cardiac procedure in past year	1,556 (<1)	1,528 (<1)
Congenital heart disease	5,053 (<1)	5,063 (<1)
Cerebrovascular disease	14,098 (1)	14,070 (1)
Arterial disease	11,397 (1)	11,381 (1)
Arrhythmia	22,688 (2)	22,749 (2)
Venous thromboembolism	12,111 (1)	12,021 (1)
Renal disease	6,854 (1)	6,744 (1)
Liver disease	11,315 (1)	11,213 (1)
Chronic lung disease	90,980 (8)	90,234 (8)
Serious neurologic disease	7,872 (1)	7,833 (1)
Rheumatic disease	20,106 (2)	20,131 (2)
Cancer	31,859 (3)	32,055 (3)
Other endstage illness	2,865 (<1)	2,754 (<1)
Alcohol-/drug abuse	38,588 (4)	38,206 (3)
Dementia	1,043 (<1)	1,035 (<1)
Hospital contact for injury/poisoning in past year	153,269 (14)	152,450 (14)
Prescription drugs used in past year		
ARB/ACE-I	65,598 (6)	65,702 (6)

Calcium channel blocker	36,896 (3)	36,966 (3)
Loop diuretics	26,308 (2)	26,436 (2)
Other diuretics	64,502 (6)	64,630 (6)
Beta-blockers	51,255 (5)	51,279 (5)
Anti-arrhythmics class I and III	1,266 (<1)	1,333 (<1)
Digoxin	2,929 (<1)	3,032 (<1)
Nitrates	9,165 (1)	9,188 (1)
Platelet inhibitors	36,732 (3)	36,641 (3)
Anticoagulants	6,089 (1)	6,064 (1)
Lipid lowering drugs	44,913 (4)	45,255 (4)
Oral antidiabetic drugs	15,959 (1)	15,706 (1)
Insulin	12,018 (1)	11,914 (1)
Antidepressants	110,539 (10)	110,576 (10)
Antipsychotics	24,927 (2)	24,797 (2)
Anxiolytics, hypnotics and sedatives	153,609 (14)	154,507 (14)
Beta-2 agonist inhalants	117,976 (11)	117,463 (11)
Corticosteroid inhalants	109,452 (10)	108,424 (10)
Xantines	6,343 (1)	6,346 (1)
Anticholinergic inhalants	10,900 (1)	10,506 (1)
Oral corticosteroids	73,158 (7)	72,790 (7)
NSAIDs	290,236 (26)	289,082 (26)
Opiates	96,805 (9)	97,464 (9)
Drugs for alcohol/opiate dependence	10,205 (1)	10,141 (1)
Antiepileptics	21,763 (2)	21,519 (2)
Dopaminergic antiparkinson drugs	2,574 (<1)	2,633 (<1)
Systemic hormone replacement therapy	98,082 (9)	98,072 (9)
Number of drugs used		
1-2	386,451 (35)	386,788 (35)
3-5	382,923 (35)	383,272 (35)
6-9	211,576 (19)	212,343 (19)
≥ 10	121,469 (11)	120,016 (11)
Health care use		
Cardiovascular emergency visits/hospitalizations in past year		
0	1,085,391 (98)	1,085,396 (98)
1	8,315 (1)	8,234 (1)
≥ 2	8,713 (1)	8,789 (1)
Other emergency visits/hospitalizations in past year		
0	834,121 (76)	835,733 (76)
1	91,912 (8)	90,914 (8)
≥ 2	176,386 (16)	175,772 (16)
Cardiovascular outpatient hospital contacts in past year		
0	1,080,144 (98)	1,080,206 (98)
1	9,653 (1)	9,600 (1)
≥ 2	12,622 (1)	12,613 (1)
Other outpatient hospital contacts in past year		
0	771,450 (70)	772,214 (70)
1	68,497 (6)	68,474 (6)
≥ 2	262,472 (24)	261,731 (24)
Emergency visit in past 7 days	4,677 (<1)	4,500 (<1)
Emergency visit in past 30 days	16,210 (1)	15,851 (1)

ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug.

Table S5. Baseline Characteristics of Azithromycin and Amoxicillin Users, Matched 1:1 According to Propensity Score.

	Azithromycin (N = 647,822)	Amoxicillin (N = 647,822)
Demographic characteristics		
Male sex	232,905 (36)	235,152 (36)
Age, mean (SD)	43.9 (12.8)	43.9 (12.7)
Country of birth		
Denmark	587,480 (91)	587,792 (91)
Europe	16,856 (3)	16,852 (3)
Other	43,486 (7)	43,178 (7)
Region of residence		
Greater Copenhagen	191,643 (30)	190,342 (29)
Zealand	97,795 (15)	97,021 (15)
Southern Denmark	177,119 (27)	178,689 (28)
Central Denmark	117,648 (18)	119,701 (18)
North Denmark	63,617 (10)	62,069 (10)
Degree of urbanization, population density/km ²		
≤ 49 inhabitants	42,776 (7)	42,847 (7)
50-99 inhabitants	172,034 (27)	171,252 (26)
100-199 inhabitants	144,077 (22)	145,807 (23)
≥ 200 inhabitants	60,953 (9)	61,350 (9)
Residence in Copenhagen suburbs	157,811 (24)	156,247 (24)
Residence in Copenhagen	70,171 (11)	70,319 (11)
Calendar year		
1997-1998	96,905 (15)	95,557 (15)
1999-2000	96,276 (15)	93,583 (14)
2001-2002	91,771 (14)	90,926 (14)
2003-2004	84,493 (13)	84,890 (13)
2005-2006	86,386 (13)	87,934 (14)
2007-2008	95,983 (15)	97,570 (15)
2009-2010	96,008 (15)	97,362 (15)
Season		
March-May	163,512 (25)	163,544 (25)
June-August	120,562 (19)	121,888 (19)
September-November	162,816 (25)	163,588 (25)
December-February	200,932 (31)	198,802 (31)
Medical history		
Acute coronary syndrome	11,741 (2)	11,866 (2)
Other ischemic heart disease	24,597 (4)	24,875 (4)
Heart failure/cardiomyopathy	6,768 (1)	7,196 (1)
Valve disorders	3,055 (<1)	3,552 (1)
Cardiac surgery/invasive cardiac procedure in past year	1,528 (<1)	1,642 (<1)
Congenital heart disease	4,249 (1)	4,477 (1)
Cerebrovascular disease	11,567 (2)	11,770 (2)
Arterial disease	9,652 (1)	9,710 (1)
Arrhythmia	17,516 (3)	17,743 (3)
Venous thromboembolism	8,764 (1)	8,938 (1)
Renal disease	5,420 (1)	5,478 (1)
Liver disease	9,002 (1)	8,966 (1)
Chronic lung disease	60,562 (9)	60,278 (9)
Serious neurologic disease	7,033 (1)	7,022 (1)
Rheumatic disease	13,396 (2)	13,306 (2)
Cancer	23,916 (4)	23,774 (4)
Other endstage illness	1,470 (<1)	1,477 (<1)
Alcohol-/drug abuse	25,378 (4)	25,625 (4)
Dementia	925 (<1)	950 (<1)
Hospital contact for injury/poisoning in past year	81,302 (13)	80,469 (12)
Prescription drugs used in past year		
ARB/ACE-I	52,196 (8)	52,363 (8)

Calcium channel blocker	30,316 (5)	30,381 (5)
Loop diuretics	22,090 (3)	22,516 (3)
Other diuretics	48,818 (8)	48,856 (8)
Beta-blockers	40,141 (6)	40,292 (6)
Anti-arrythmics class I and III	1,118 (<1)	1,155 (<1)
Digoxin	2,710 (<1)	2,890 (<1)
Nitrates	7,869 (1)	8,005 (1)
Platelet inhibitors	31,688 (5)	31,902 (5)
Anticoagulants	5,877 (1)	6,206 (1)
Lipid lowering drugs	37,288 (6)	37,292 (6)
Oral antidiabetic drugs	13,295 (2)	13,271 (2)
Insulin	9,126 (1)	9,234 (1)
Antidepressants	74,707 (12)	74,339 (11)
Antipsychotics	19,637 (3)	19,763 (3)
Anxiolytics, hypnotics and sedatives	108,297 (17)	107,642 (17)
Beta-2 agonist inhalants	76,292 (12)	75,393 (12)
Corticosteroid inhalants	72,270 (11)	71,616 (11)
Xantines	5,520 (1)	5,617 (1)
Anticholinergic inhalants	8,907 (1)	9,038 (1)
Oral corticosteroids	50,010 (8)	49,697 (8)
NSAIDs	192,922 (30)	191,020 (29)
Opiates	73,853 (11)	73,555 (11)
Drugs for alcohol/opiate dependence	8,217 (1)	8,165 (1)
Antiepileptics	17,365 (3)	17,324 (3)
Dopaminergic antiparkinson drugs	2,069 (<1)	2,061 (<1)
Systemic hormone replacement therapy	59,902 (9)	59,359 (9)
Number of drugs used		
1-2	203,626 (31)	207,183 (32)
3-5	223,105 (34)	222,195 (34)
6-9	136,515 (21)	134,422 (21)
≥ 10	84,576 (13)	84,022 (13)
Health care use		
Cardiovascular emergency visits/ hospitalizations in past year		
0	633,653 (98)	633,496 (98)
1	6,766 (1)	6,768 (1)
≥ 2	7,403 (1)	7,558 (1)
Other emergency visits/ hospitalizations in past year		
0	483,432 (75)	485,306 (75)
1	51,927 (8)	51,245 (8)
≥ 2	112,463 (17)	111,271 (17)
Cardiovascular outpatient hospital contacts in past year		
0	629,644 (97)	629,554 (97)
1	7,838 (1)	7,835 (1)
≥ 2	10,340 (2)	10,433 (2)
Other outpatient hospital contacts in past year		
0	419,858 (65)	422,540 (65)
1	45,117 (7)	44,519 (7)
≥ 2	182,847 (28)	180,763 (28)
Emergency visit in past 7 days	3,023 (<1)	3,051 (<1)
Emergency visit in past 30 days	8,963 (1)	8,908 (1)

Table S6. Risk of Cardiovascular Death Comparing Users of Azithromycin and Amoxicillin Matched 1:1 According to Propensity Score.

	Azithromycin (n=647,822)	Amoxicillin (n=647,822)
Current use ^a		
Events, No.	12	20
Rate per 1000 P-Y	1.4	2.3
Rate Ratio (95% CI)	0.60 (0.29-1.23)	
Recent use ^b		
Events, No.	6	13
Rate per 1000 P-Y	0.7	1.6
Rate Ratio (95% CI)	0.46 (0.17-1.21)	
Past use ^c		
Events, No.	18	24
Rate per 1000 P-Y	0.5	0.6
Rate Ratio (95% CI)	0.72 (0.39-1.33)	

Abbreviations: P-Y, person-years; CI, confidence interval.

^aDays 1-5 following treatment initiation.

^bDays 6-10.

^cDays 11-30.

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