

Appendix: Use of Clarithromycin and Roxithromycin and the Risk of Cardiac Death

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Table A. Exclusion conditions with ICD, ATC, and NCSP codes.

Condition^{ab}	ICD codes
Cancer	ICD-8: 140-199, 170-179, 200-207; ICD-10: C00-43, C44-97
HIV/AIDS	ICD-8: 07983; ICD-10: B20-B24, Z21
End stage renal disease	ICD-8: 792; ICD-10: N185, Z490-492, Z992
Liver disease	ICD-8: 570-573; ICD-10: K70-74, K762-767
Serious neurologic disease	ICD-8: 330-332, 340-341, 344, 348; ICD-10: G10-G14, G35-G37, G71, G82
Congenital anomalies/childhood conditions	ICD-8: 27309, 313-314, 343, 741-743, 746, 74709, 74719, 74729, 74739; ICD-10: E84, F711, F72, F73, F781, F791, G51, G80, Q01-Q03, Q05, Q20-Q26, Q90
Other endstage illness	ICD-8: 267-268, 445, 78009; ICD-10: E105B, E115B, E40-43, I702A, R029, R402, R64, Z991
Dementia	ICD-8: 290, 293, 794; ICD-10: F00-F03, G30; ATC: N06D
Drug abuse	ICD-8: 304, 971; ICD-10: F11-16, F18-19, R781-785, T40; ATC: N07BC
Alcohol abuse	ICD-8: 303; ICD-10: F10, T40
Psychosis	ICD10: F20-F29
Organ transplant	NCSP: KKAS, KFQA, KFQB, KJJC, KGDG, KJLE

ICD, international classification of diseases; ATC, anatomic therapeutic chemical; NCSP, Nordic Classification of Surgical procedures

^a Data from the National Patient Register.

^b Data from the National Prescription Register.

Table B. ICD codes for study outcome.

Cause of death^a	ICD-10 codes
Cardiac	I11, I13, I20-25, I27, I30-52

ICD, international classification of diseases.

^a Data from The Danish Register of Causes of Death.

Table C. Covariates included in propensity score with ICD, ATC, and NCSP codes.

Covariate	Codes
Demographic characteristics^a	
Sex	
Age (5-year intervals)	
Country of birth (Denmark, Rest of Europe, Outside Europe)	
Calendar year (5-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	NCSP: KF
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
Renal disease	ICD-8: 403-404, 792, 580-584, 59309-59329; ICD-10: I12-13, N00-08, N17-19, N25, Z49, Z940, Z992
Serious respiratory disease	ICD-8: 426, 517, 570-573; ICD-10: E662, I27, J961, J969, J84, R092
Other respiratory disease	ICD-8: 490-493, 515-519; ICD-10: J40-47, J60-70, J92, J96, J982, J983
Other psychiatric disorder	ICD-8: 291-292, 294-302, 305-315; ICD-10: F04-F09, F30-F99
Prescription drugs used in past year^c	
	ATC codes
ARB/ACE-I	C09A-D
Dihydropyridine CCB	C08C
Non-dihydropyridine CCB	C08D
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
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Table C continued.	
Corticosteroid inhalants	R03BA, R03AK
Xantines	R03DA
Anticholinergic inhalants	R03BB
Oral corticosteroids	H02AB
NSAIDs	M01A
Opiates	N02A
Systemic hormone replacement therapy	G03CA03, G03CA04, G03CA53, G03CA57, G03FA01, G03FA11, G03FA12, G03FA15, G03FA17, G03FB01, G03FB05, G03FB06, G03FB09, G03FB11, G03HB01, G03XC01, G03DC05, G03CX01
Anti-osteoporotic drugs	G03XC01, H05AA02, M05BA, M05BB, M05BX03, M05BX04
PPI/H2-blocker	A02B
Number of drugs used (1-5; 6-9; ≥ 10)	
Health care use in the past 6 months^b	
Cardiovascular ED visit/hospitalisation (yes/no)	
Other ED visit/hospitalisation (yes/no)	
Cardiovascular outpatient hospital contact (yes/no)	
Other outpatient hospital contact (yes/no)	
ED visit in past 7 days (yes/no)	

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

^a Data from the Central Person Register.

^b Data from the National Patient Register.

^c Data from the National Prescription Register.

Table D. ATC codes for CYP3A inhibiting drugs.

Drug^a	ATC code
Aprepitant	A04AD12
Verapamil	C08DA01
Diltiazem	C08DB01
Ketoconazol	J02AB02
Fluconazol	J02AC01
Itraconazol	J02AC02
Saquinavir	J05AE01
Indinavir	J05AE02
Ritonavir	J05AE03
Nelfinavir	J05AE04
Nefazodon	N06AX06

ATC, anatomic therapeutic chemical.

^a Data from the National Prescription Register.

Table E. Standardised differences between participants with use of clarithromycin, roxithromycin, and penicillin V included in analysis.

	Standardised differences (%) ^a		
	Roxithromycin vs. Penicillin V	Clarithromycin vs. Penicillin V	Clarithromycin vs. Roxithromycin
Male sex	-12.9	-10.4	2.5
Age group			
40-44	-5.1	-9.6	-4.5
45-49	-2.8	-5.2	-2.4
50-54	-3.2	-2.9	0.3
55-59	-0.9	0.5	1.4
60-64	3.1	4.1	1.0
65-69	5.0	6.9	1.9
70-74	5.6	8.0	2.5
Place of birth^a			
Denmark	0.0	-0.5	-0.5
Rest of Europe	1.1	1.4	0.3
Outside Europe	-0.8	-0.5	0.4
Calendar year			
1997-2001	-32.4	3.3	35.8
2002-2006	-4.1	-0.8	3.3
2007-2011	32.3	-2.6	-34.9
Season			
March-May	-3.1	-0.5	2.6
June-August	-11.4	-13.2	-1.8
September-November	3.3	1.8	-1.5
December-February	9.5	10.0	0.5
Medical history			
Acute coronary syndrome	1.8	2.3	0.5
Other ischemic heart disease	5.3	5.4	0.1
Heart failure/ cardiomyopathy	2.9	3.7	0.8
Valve disorders	1.1	0.3	-0.8
Cerebrovascular disease	2.0	1.3	-0.6
Arterial disease	2.9	3.6	0.7
Arrhythmia	4.2	2.8	-1.3
Renal disease	2.0	1.5	-0.5
Serious respiratory disease	5.2	8.2	3.1
Other respiratory disease	18.4	24.2	5.8
Psychiatric disorder	4.6	3.5	-1.2
Cardiac surgery in the last year	-0.8	0.1	0.9
Prescription drug use in the last year			
ARB/ACE-I	8.5	3.9	-4.6
Dihydropyridine CCB	4.6	0.8	-3.8
Non-dihydropyridine CCB	1.7	3.6	1.9
Loop diuretics	6.1	8.9	2.8
Other diuretics	6.2	4.4	-1.8
Beta-blockers	3.0	0.5	-2.5
Anti-arrhythmics class I and III	0.4	0.9	0.5
Digoxin	0.2	1.3	1.1

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Table E continued.

	Roxithromycin vs. Penicillin V	Clarithromycin vs. Penicillin V	Clarithromycin vs. Roxithromycin
Nitrates	2.4	4.2	1.8
Platelet inhibitors	6.4	3.9	-2.5
Anticoagulants	0.7	-1.2	-1.9
Lipid lowering drugs	10.1	1.6	-8.5
Oral antidiabetic drugs	2.9	-0.4	-3.3
Insulin	0.9	-0.6	-1.5
Antidepressants	6.3	4.6	-1.7
Antipsychotics	-0.6	-0.4	0.1
Anxiolytics, hypnotics and sedatives	4.8	11.2	6.5
Beta-2 agonist inhalants	17.2	24.3	7.2
Corticosteroid inhalants	20.7	28.9	8.2
Xantines	5.0	10.9	6.1
Anticholinergic inhalants	12.7	15.2	2.6
Oral corticosteroids	12.3	17.7	5.5
NSAIDs	1.8	-0.7	-2.5
Opiates	6.5	7.1	0.6
Systemic hormone replacement therapy	4.7	11.3	6.6
Anti-osteoporotic drugs	6.1	7.0	0.9
PPI/H2-blocker	11.3	21.8	10.5
No. of prescription drugs used in the last year			
1-5	-22.6	-28.6	-6.0
6-9	8.8	9.7	1.0
≥ 10	19.7	25.9	6.2
Use of health care in the last 6 months			
Cardiovascular ED visit/hospitalisation	1.3	2.1	0.8
Other ED visit/hospitalisation	0.7	1.5	0.8
Cardiovascular outpatient contact	1.6	1.4	-0.2
Other outpatient contact	13.1	10.8	-2.3

ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor;

NSAID, non-steroidal anti-inflammatory drug. ED, emergency department.

^a Covariates were considered well balanced if the standardized difference was less than 10%.

Table F. Odds ratios in propensity score models for clarithromycin and roxithromycin versus penicillin V.

Parameter	Odds Ratio (95% CI)	
	Roxithromycin	Clarithromycin
Male sex	0.81 (0.80-0.81)	0.89 (0.88-0.90)
Age group		
40-44	1.00 (Reference)	1.00 (Reference)
45-49	1.04 (1.03-1.05)	1.08 (1.06-1.10)
50-54	1.03 (1.02-1.04)	1.11 (1.09-1.13)
55-59	1.04 (1.03-1.05)	1.17 (1.15-1.19)
60-64	1.07 (1.06-1.08)	1.24 (1.21-1.26)
65-69	1.11 (1.09-1.12)	1.28 (1.25-1.30)
70-74	1.13 (1.11-1.14)	1.27 (1.25-1.30)
Place of birth^a		
Denmark	1.00 (Reference)	1.00 (Reference)
Rest of Europe	1.07 (1.05-1.09)	1.10 (1.07-1.14)
Outside Europe	0.89 (0.88-0.90)	0.98 (0.96-1.01)
Calendar year		
1997-2001	1.00 (Reference)	1.00 (Reference)
2002-2006	1.66 (1.65-1.68)	0.92 (0.91-0.93)
2007-2011	2.56 (2.54-2.58)	0.88 (0.87-0.90)
Season		
March-May	1.00 (Reference)	1.00 (Reference)
June-August	0.84 (0.83-0.85)	0.77 (0.76-0.78)
September-November	1.11 (1.11-1.12)	1.03 (1.02-1.05)
December-February	1.22 (1.21-1.23)	1.16 (1.15-1.18)
Medical history		
Acute coronary syndrome	0.99 (0.97-1.00)	0.98 (0.95-1.01)
Other ischemic heart disease	1.06 (1.05-1.08)	1.08 (1.06-1.11)
Heart failure/ cardiomyopathy	0.95 (0.93-0.97)	0.96 (0.92-1.00)
Valve disorders	1.00 (0.97-1.03)	0.94 (0.89-1.00)
Cerebrovascular disease	0.97 (0.96-0.99)	0.96 (0.93-0.99)
Arterial disease	1.01 (1.00-1.03)	1.06 (1.02-1.09)
Arrhythmia	1.08 (1.06-1.09)	1.06 (1.03-1.09)
Renal disease	1.03 (1.00-1.06)	1.00 (0.95-1.05)
Serious respiratory disease	1.04 (1.01-1.07)	1.20 (1.15-1.26)
Other respiratory disease	1.20 (1.19-1.22)	1.25 (1.23-1.28)
Psychiatric disorder	1.07 (1.06-1.09)	1.02 (1.00-1.05)
Cardiac surgery in the last year	0.83 (0.79-0.87)	0.94 (0.87-1.02)
Prescription drug use in the last year		
ARB/ACE-I	0.99 (0.98-1.00)	1.01 (1.00-1.03)
Dihydropyridine CCB	0.95 (0.94-0.96)	0.89 (0.87-0.91)
Non-dihydropyridine CCB	0.97 (0.95-0.99)	0.92 (0.89-0.96)
Loop diuretics	0.98 (0.97-1.00)	0.95 (0.93-0.98)
Other diuretics	0.97 (0.96-0.98)	0.89 (0.88-0.90)
Beta-blockers	0.94 (0.93-0.95)	0.92 (0.91-0.94)
Anti-arrhythmics class I and III	0.94 (0.90-0.99)	0.99 (0.91-1.08)
Digoxin	0.91 (0.89-0.94)	0.86 (0.82-0.90)
Nitrates	0.98 (0.97-1.00)	0.93 (0.90-0.96)

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Table F continued.

	Roxithromycin	Clarithromycin
Platelet inhibitors	0.95 (0.94-0.96)	0.91 (0.89-0.92)
Anticoagulants	0.85 (0.83-0.87)	0.76 (0.73-0.79)
Lipid lowering drugs	0.97 (0.96-0.98)	0.92 (0.91-0.94)
Oral antidiabetic drugs	0.93 (0.92-0.94)	0.85 (0.83-0.88)
Insulin	0.89 (0.88-0.91)	0.86 (0.82-0.89)
Antidepressants	0.95 (0.94-0.95)	0.91 (0.90-0.93)
Antipsychotics	0.82 (0.81-0.84)	0.74 (0.72-0.76)
Anxiolytics, hypnotics and sedatives	0.98 (0.98-0.99)	0.99 (0.97-1.00)
Beta-2 agonist inhalants	1.12 (1.11-1.14)	1.09 (1.07-1.11)
Corticosteroid inhalants	1.23 (1.21-1.24)	1.38 (1.36-1.41)
Xantines	1.09 (1.06-1.12)	1.06 (1.02-1.10)
Anticholinergic inhalants	1.10 (1.08-1.12)	1.19 (1.16-1.23)
Oral corticosteroids	1.13 (1.11-1.14)	1.14 (1.12-1.16)
NSAIDs	0.90 (0.90-0.91)	0.85 (0.84-0.86)
Opiates	0.95 (0.94-0.96)	0.91 (0.90-0.93)
Systemic hormone replacement therapy	0.98 (0.97-0.99)	1.07 (1.05-1.08)
Anti-osteoporotic drugs	0.94 (0.93-0.96)	1.02 (0.98-1.05)
PPI/H2-blocker	1.06 (1.05-1.07)	1.41 (1.39-1.43)
No. of prescription drugs used in the last year		
1-5	1.00 (Reference)	1.00 (Reference)
6-9	1.32 (1.31-1.33)	1.41 (1.39-1.43)
≥ 10	1.64 (1.62-1.66)	1.87 (1.84-1.91)
Use of health care in the last 6 months		
Cardiovascular ED visit/hospitalisation	0.98 (0.95-1.00)	1.01 (0.96-1.05)
Other ED visit/hospitalisation	0.99 (0.98-1.00)	0.94 (0.92-0.96)
Cardiovascular outpatient contact	0.95 (0.93-0.97)	0.93 (0.90-0.96)
Other outpatient contact	1.07 (1.06-1.08)	1.13 (1.11-1.14)
ED visit in the last 7 days	0.39 (0.38-0.41)	0.32 (0.29-0.35)

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

Table G. Odds ratios in risk score model for cardiac mortality.

Parameter	Odds Ratio (95% CI)
Male sex	1.95 (1.49-2.56)
Age group	
40-44	1.00 (Reference)
45-49	0.77 (0.17-3.43)
50-54	4.74 (1.62-13.85)
55-59	5.69 (1.99-16.29)
60-64	8.99 (3.21-25.21)
65-69	13.09 (4.71-36.38)
70-74	22.03 (7.99-60.79)
Place of birth^a	
Denmark	1.00 (Reference)
Rest of Europe	1.10 (0.49-2.47)
Outside Europe	0.92 (0.43-1.96)
Calendar year	
1997-2001	1.00 (Reference)
2002-2006	0.91 (0.69-1.20)
2007-2011	0.55 (0.39-0.78)
Season	
March-May	1.00 (Reference)
June-August	1.78 (1.22-2.61)
September-November	1.61 (1.11-2.35)
December-February	2.01 (1.42-2.85)
Medical history	
Acute coronary syndrome	1.49 (1.01-2.18)
Other ischemic heart disease	0.94 (0.64-1.36)
Heart failure/ cardiomyopathy	1.70 (1.17-2.47)
Valve disorders	1.42 (0.82-2.48)
Cerebrovascular disease	1.29 (0.88-1.90)
Arterial disease	1.30 (0.88-1.92)
Arrhythmia	0.92 (0.62-1.39)
Renal disease	1.27 (0.66-2.43)
Serious respiratory disease	1.07 (0.57-1.98)
Other respiratory disease	1.40 (0.96-2.03)
Psychiatric disorder	0.84 (0.47-1.51)
Cardiac surgery in the last year	0.47 (0.17-1.32)
Prescription drug use in the last year	
ARB/ACE-I	1.17 (0.87-1.56)
Dihydropyridine CCB	1.39 (1.00-1.93)
Non-dihydropyridine CCB	1.24 (0.81-1.91)
Loop diuretics	3.97 (2.85-5.53)
Other diuretics	0.98 (0.73-1.30)
Beta-blockers	0.97 (0.70-1.34)
Anti-arrhythmics class I and III	1.93 (1.04-3.58)
Digoxin	1.81 (1.20-2.72)
Nitrates	1.40 (0.96-2.05)
Platelet inhibitors	1.03 (0.75-1.42)
Anticoagulants	0.92 (0.58-1.47)

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Table G continued.	
Lipid lowering drugs	0.80 (0.57-1.14)
Oral antidiabetic drugs	1.35 (0.92-1.99)
Insulin	0.88 (0.50-1.55)
Antidepressants	0.88 (0.61-1.28)
Antipsychotics	2.65 (1.74-4.04)
Anxiolytics, hypnotics and sedatives	1.15 (0.87-1.52)
Beta-2 agonist inhalants	0.76 (0.50-1.15)
Corticosteroid inhalants	1.00 (0.66-1.52)
Xantines	1.04 (0.54-2.00)
Anticholinergic inhalants	1.16 (0.67-1.99)
Oral corticosteroids	1.01 (0.68-1.48)
NSAIDs	0.73 (0.55-0.96)
Opiates	1.27 (0.92-1.74)
Systemic hormone replacement therapy	0.50 (0.28-0.90)
Anti-osteoporotic drugs	0.97 (0.47-2.01)
PPI/H2-blocker	0.79 (0.57-1.10)
No. of prescription drugs used in the last year	
1-5	1.00 (Reference)
6-9	1.22 (0.87-1.72)
≥ 10	0.75 (0.46-1.24)
Use of health care in the last 6 months	
Cardiovascular ED visit/hospitalisation	1.74 (1.08-2.79)
Other ED visit/hospitalisation	1.36 (0.94-1.96)
Cardiovascular outpatient contact	0.84 (0.51-1.39)
Other outpatient contact	0.74 (0.55-1.01)
ED visit in the last 7 days	1.06 (0.38-2.96)

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

Table H. Baseline characteristics of participants with use of clarithromycin and penicillin V, matched 1:2 on propensity score.

	Clarithromycin (n = 160,297)	Penicillin V (n = 320,594)
Number of individuals	108,767	262,694
Male sex	58,608 (36.6)	116,994 (36.5)
Age, mean (SD)	57.2 (9.6)	57.2 (9.6)
Age group		
40-44	21,506 (13.4)	42,344 (13.2)
45-49	22,078 (13.8)	44,083 (13.8)
50-54	24,833 (15.5)	49,327 (15.4)
55-59	26,947 (16.8)	53,969 (16.8)
60-64	25,386 (15.8)	51,444 (16.0)
65-69	21,512 (13.4)	43,434 (13.5)
70-74	18,035 (11.3)	35,993 (11.2)
Place of birth		
Denmark	148,842 (92.9)	297,735 (92.9)
Rest of Europe	4,127 (2.6)	8,229 (2.6)
Outside Europe	7,328 (4.6)	14,630 (4.6)
Calendar year		
1997-2001	53,559 (33.4)	106,962 (33.4)
2002-2006	54,146 (33.8)	108,099 (33.7)
2007-2011	52,592 (32.8)	105,533 (32.9)
Season		
March-May	40,446 (25.2)	81,457 (25.4)
June-August	26,194 (16.3)	50,679 (15.8)
September-November	39,991 (24.9)	80,143 (25.0)
December-February	53,666 (33.5)	108,315 (33.8)
Medical history		
Acute coronary syndrome	6,739 (4.2)	13,587 (4.2)
Other ischemic heart disease	13,629 (8.5)	27,137 (8.5)
Heart failure/ cardiomyopathy	3,772 (2.4)	7,445 (2.3)
Valve disorders	1,262 (0.8)	2,457 (0.8)
Cerebrovascular disease	5,367 (3.3)	10,925 (3.4)
Arterial disease	5,167 (3.2)	10,409 (3.2)
Arrhythmia	7,625 (4.8)	15,209 (4.7)
Renal disease	1,419 (0.9)	2,839 (0.9)
Serious respiratory disease	2,449 (1.5)	4,607 (1.4)
Other respiratory disease	24,642 (15.4)	47,847 (14.9)
Psychiatric disorder	6,254 (3.9)	12,658 (3.9)
Cardiac surgery in the last year	656 (0.4)	1,308 (0.4)
Prescription drug use in the last year		
ARB/ACE-I	25,884 (16.1)	52,292 (16.3)
Dihydropyridine CCB	12,022 (7.5)	24,327 (7.6)
Non-dihydropyridine CCB	3,787 (2.4)	7,502 (2.3)
Loop diuretics	11,835 (7.4)	23,500 (7.3)
Other diuretics	23,503 (14.7)	47,547 (14.8)
Beta-blockers	16,661 (10.4)	34,038 (10.6)
Anti-arrhythmics class I and III	636 (0.4)	1,263 (0.4)
Digoxin	2,019 (1.3)	4,020 (1.3)

Table continues on the next page.

Table H continued.

	Clarithromycin	Penicillin V
Nitrates	5,093 (3.2)	10,154 (3.2)
Platelet inhibitors	18,861 (11.8)	37,902 (11.8)
Anticoagulants	2,754 (1.7)	5,509 (1.7)
Lipid lowering drugs	19,087 (11.9)	38,429 (12.0)
Oral antidiabetic drugs	6,282 (3.9)	12,498 (3.9)
Insulin	2,936 (1.8)	6,028 (1.9)
Antidepressants	21,213 (13.2)	42,549 (13.3)
Antipsychotics	4,974 (3.1)	10,029 (3.1)
Anxiolytics, hypnotics and sedatives	38,501 (24.0)	77,683 (24.2)
Beta-2 agonist inhalants	29,464 (18.4)	57,856 (18.0)
Corticosteroid inhalants	32,736 (20.4)	63,968 (20.0)
Xantines	3,537 (2.2)	6,705 (2.1)
Anticholinergic inhalants	6,490 (4.0)	12,138 (3.8)
Oral corticosteroids	19,598 (12.2)	38,236 (11.9)
NSAIDs	51,520 (32.1)	102,938 (32.1)
Opiates	23,073 (14.4)	46,580 (14.5)
Systemic hormone replacement therapy	25,331 (15.8)	51,157 (16.0)
Anti-osteoporotic drugs	3,874 (2.4)	7,658 (2.4)
PPI/H2-blocker	35,083 (21.9)	70,732 (22.1)
No. of prescription drugs used in the last year		
1-5	83,350 (52.0)	164,925 (51.4)
6-9	40,501 (25.3)	83,575 (26.1)
≥ 10	36,446 (22.7)	72,094 (22.5)
Use of health care in the last 6 months		
Cardiovascular ED visit/hospitalisation	3,084 (1.9)	6,186 (1.9)
Other ED visit/hospitalisation	17,310 (10.8)	34,594 (10.8)
Cardiovascular outpatient contact	3,849 (2.4)	7,617 (2.4)
Other outpatient contact	40,786 (25.4)	81,872 (25.5)
ED visit in the last 7 days	512 (0.3)	968 (0.3)

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

Table I. Baseline characteristics of participants with use of roxithromycin and penicillin V, matched 1:2 on propensity score.

	Roxithromycin (n = 588,988)	Penicillin V (n = 1,177,498)
Number of individuals	350,575	716,872
Male sex	208,343 (35.4)	419,009 (35.6)
Age, mean (SD)	56.6 (9.7)	56.6 (9.7)
Age group		
40-44	88,353 (15.0)	177,420 (15.1)
45-49	86,122 (14.6)	172,155 (14.6)
50-54	90,525 (15.4)	180,726 (15.3)
55-59	95,888 (16.3)	191,012 (16.2)
60-64	91,146 (15.5)	182,358 (15.5)
65-69	75,181 (12.8)	149,941 (12.7)
70-74	61,773 (10.5)	123,886 (10.5)
Place of birth		
Denmark	547,639 (93.0)	1,094,008 (92.9)
Rest of Europe	14,855 (2.5)	29,845 (2.5)
Outside Europe	26,494 (4.5)	53,645 (4.6)
Calendar year		
1997-2001	106,094 (18.0)	208,913 (17.7)
2002-2006	189,820 (32.2)	383,970 (32.6)
2007-2011	293,074 (49.8)	584,615 (49.6)
Season		
March-May	142,047 (24.1)	283,250 (24.1)
June-August	100,223 (17.0)	198,179 (16.8)
September-November	150,821 (25.6)	302,928 (25.7)
December-February	195,897 (33.3)	393,141 (33.4)
Medical history		
Acute coronary syndrome	24,156 (4.1)	48,554 (4.1)
Other ischemic heart disease	49,934 (8.5)	99,923 (8.5)
Heart failure/ cardiomyopathy	13,178 (2.2)	26,412 (2.2)
Valve disorders	5,047 (0.9)	10,171 (0.9)
Cerebrovascular disease	20,403 (3.5)	40,890 (3.5)
Arterial disease	18,310 (3.1)	36,553 (3.1)
Arrhythmia	29,728 (5.0)	59,907 (5.1)
Renal disease	5,515 (0.9)	11,133 (0.9)
Serious respiratory disease	6,919 (1.2)	13,473 (1.1)
Other respiratory disease	78,485 (13.3)	153,694 (13.1)
Psychiatric disorder	24,346 (4.1)	48,784 (4.1)
Cardiac surgery in the last year	2,098 (0.4)	4,225 (0.4)
Prescription drug use in the last year		
ARB/ACE-I	105,302 (17.9)	212,307 (18.0)
Dihydropyridine CCB	50,266 (8.5)	101,301 (8.6)
Non-dihydropyridine CCB	12,236 (2.1)	24,469 (2.1)
Loop diuretics	39,307 (6.7)	78,352 (6.7)
Other diuretics	90,091 (15.3)	181,024 (15.4)
Beta-blockers	65,721 (11.2)	133,013 (11.3)
Anti-arrhythmics class I and III	2,159 (0.4)	4,459 (0.4)
Digoxin	6,704 (1.1)	13,501 (1.1)

Table continues on the next page.

Table I continued.		
	Roxithromycin	Penicillin V
Nitrates	16,894 (2.9)	33,745 (2.9)
Platelet inhibitors	74,129 (12.6)	149,014 (12.7)
Anticoagulants	11,655 (2.0)	23,554 (2.0)
Lipid lowering drugs	87,153 (14.8)	175,252 (14.9)
Oral antidiabetic drugs	27,058 (4.6)	54,239 (4.6)
Insulin	11,999 (2.0)	24,452 (2.1)
Antidepressants	81,350 (13.8)	163,951 (13.9)
Antipsychotics	18,141 (3.1)	36,666 (3.1)
Anxiolytics, hypnotics and sedatives	125,545 (21.3)	251,994 (21.4)
Beta-2 agonist inhalants	92,409 (15.7)	182,368 (15.5)
Corticosteroid inhalants	101,348 (17.2)	198,959 (16.9)
Xantines	8,248 (1.4)	16,195 (1.4)
Anticholinergic inhalants	20,875 (3.5)	39,609 (3.4)
Oral corticosteroids	61,815 (10.5)	121,546 (10.3)
NSAIDs	196,256 (33.3)	393,428 (33.4)
Opiates	83,453 (14.2)	167,297 (14.2)
Systemic hormone replacement therapy	79,431 (13.5)	158,692 (13.5)
Anti-osteoporotic drugs	13,403 (2.3)	26,356 (2.2)
PPI/H2-blocker	104,313 (17.7)	209,470 (17.8)
No. of prescription drugs used in the last year		
1-5	323,735 (55.0)	644,533 (54.7)
6-9	146,273 (24.8)	297,382 (25.3)
≥ 10	118,980 (20.2)	235,583 (20.0)
Use of health care in the last 6 months		
Cardiovascular ED visit/hospitalisation	10,680 (1.8)	21,538 (1.8)
Other ED visit/hospitalisation	62,136 (10.5)	124,192 (10.5)
Cardiovascular outpatient contact	14,350 (2.4)	28,889 (2.5)
Other outpatient contact	155,873 (26.5)	312,368 (26.5)
ED visit in the last 7 days	2,309 (0.4)	4,182 (0.4)

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

Table J. Distribution for the number of previous courses (%) by study drug.

Number of previous courses	Roxithromycin	Clarithromycin	Penicillin V
	(n=588,988)	(n=160,297)	(n=4,355,309)
0	157,714 (27)	48,514 (30)	1,439,732 (33)
1	111,169 (19)	31,612 (20)	903,853 (21)
2	80,559 (14)	21,382 (13)	592,434 (14)
3	58,483 (10)	14,704 (9)	400,826 (9)
4	43,024 (7)	10,681 (7)	276,396 (6)
5	31,834 (5)	7723 (5)	193,860 (4)
6	24,066 (4)	5696 (4)	138,768 (3)
7	18,171 (3)	4256 (3)	100,640 (2)
8	14,034 (2)	3231 (2)	73,714 (2)
9	10,711 (2)	2509 (2)	54,769 (1)
10	8345 (1)	1916 (1)	40,960 (1)
11	6480 (1)	1609 (1)	30,839 (1)
12	5043 (1)	1234 (1)	23,428 (1)
13	3958 (1)	951 (1)	17,983 (<1)
14	3127 (1)	733 (<1)	13,901 (<1)
≥15	12270 (2)	3546 (2)	53,206 (1)