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Does macrolide use confer risk of out-of-hospital cardiac arrest compared with penicillin V? A Danish national case-crossover and case–time–control study

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ABSTRACT

Introduction and objectives Macrolides have been associated with proarrhythmic properties, but the evidence is conflicting. We evaluated the risk of out-of-hospital cardiac arrest (OHCA) associated with specific macrolides in a retrospective study. Associations between specific macrolides and OHCA were examined by conditional logistic regression analyses in case-crossover and case–time–control models, using penicillin-V treatment as the comparative reference. From nationwide registries, we identified all OHCAs in Denmark from 2001 to 2010 and use of antibiotics.

Ethics The present study was approved by the Danish Data Protection Agency (Danish Data Protection Agency (ref.no. 2007-58-0015, local ref.no. GEH-2014-017, (I-Suite.nr. 02 735)).

Participants We identified 29 111 patients with an OHCA. Of these, 514 were in macrolide treatment ≤7 days before OHCA and 1237 in penicillin-V treatment.

Results In the case-crossover analyses, overall macrolide use was not associated with OHCA with penicillin V as negative comparative reference (OR=0.90; 95% CI 0.73 to 1.10). Compared with penicillin-V treatment, specific macrolides were not associated with increased risk of OHCA: roxithromycin (OR=0.97; 95% CI 0.74 to 1.26), erythromycin (OR=0.68; 95% CI 0.44 to 1.06), clarithromycin (OR=0.95; 95% CI 0.61 to 1.48) and azithromycin (OR=0.85; 95% CI 0.57 to 1.27). Similar results were obtained using case–time–control models: overall macrolide use (OR=0.81; 95% CI 0.62 to 1.06) and specific macrolides (roxithromycin (OR=0.70; 95% CI 0.49 to 1.00), erythromycin (OR=0.67; 95% CI 0.38 to 1.18), clarithromycin (OR=0.75; 95% CI 0.41 to 1.39) or azithromycin (OR=1.17; 95% CI 0.70 to 1.95)).

Conclusion The risk of OHCA during treatment with macrolides was similar to that of penicillin V, suggesting no additional risk of OHCA associated with macrolides.

Strengths and limitations of this study

- Although the proarrhythmic properties of macrolide treatment may have prolonged the QT interval prior to the out-of-hospital cardiac arrest (OHCA), we are not able to prove such causation given the observational nature of the study.
- The infrequency of OHCA as outcome of this treatment limited the final study cohort and may have influenced our findings.
- We cannot rule out that incorrect diagnosing can lead to OHCA and a misinterpreted association with use of antibiotic.
- Data on specific infections, for which the drugs were prescribed, were not available for this study.
- Our current study holds the strength of enrolling members of the general population from a nationwide database containing all patients suffering from an OHCA and data on all patient usage of antibiotics.

INTRODUCTION

Macrolides are commonly used to treat a range of infections including upper and lower respiratory tract infections and sexually transmitted diseases. Moreover, macrolides are often the drug of choice in patients known to be penicillin intolerant.[1–4] However, a known possible adverse drug reaction related to macrolide treatment is prolongation of the QT interval, which increase the risk of torsades de pointes (TdP) ventricular tachycardia, a potentially fatal arrhythmia.[2 3 5 6]

To date, the cardiac risks associated with specific macrolides (ie, roxithromycin, erythromycin, clarithromycin and azithromycin) have been evaluated in several studies, but the findings have been conflicting. As such, use of erythromycin has been associated with case reports of TdP and increased risk of sudden cardiac death (SCD).[7] Azithromycin use, as compared with no treatment or treatment with a phenoxymethylpenicillin (ie, penicillin V), was previously associated with increased cardiovascular mortality while no association was found for use of clarithromycin.[2 8 9] Furthermore, azithromycin

Table 1 Characteristics for patients receiving penicillin V and macrolides

	Penicillin V	All macrolides	P value
N	1237	514	
Age, years (IQR)	68.6 (58.4–80.5)	71.3 (60.8–80.4)	0.73
Male (%)	764 (61.8)	268 (52.1)	<0.001
Income group (%)			
0 (lowest income quintile)	124 (10.0)	60 (11.7)	
1	322 (26.0)	131 (25.5)	
2	369 (29.8)	155 (30.2)	0.71
3	231 (18.7)	100 (19.5)	
4 (highest income quintile)	189 (15.3)	68 (13.2)	
Comorbidity (%)			
Diabetes	144 (11.6)	74 (14.4)	0.11
Peripheral vascular disease	50 (4.0)	24 (4.7)	0.55
Previous MI	97 (7.8)	47 (9.1)	0.37
Ischaemic heart disease	177 (14.3)	61 (11.9)	0.17
Heart failure	175 (14.2)	70 (13.6)	0.77
Atrial fibrillation	126 (10.2)	45 (8.8)	0.36
COPD	201 (16.3)	121 (23.5)	<0.001
Cancer	132 (10.7)	43 (8.4)	0.14
Depression	33 (2.7)	15 (2.9)	0.77
Any psychiatric disease	164 (13.3)	57 (11.1)	0.21
Charlson score (IQR)	0 (0–2)	1 (0–2)	0.08
Concomitant pharmacotherapy (%)			
Lipid-lowering drugs	127 (10.3)	69 (13.4)	0.06
Loop diuretics	342 (27.7)	165 (32.1)	0.06
Beta-blockers	202 (16.3)	96 (18.7)	0.23
ACE inhibitors	245 (19.8)	122 (23.7)	0.07
Vitamin K antagonists	71 (5.7)	29 (5.6)	0.94
Antiplatelets	20 (1.6)	11 (2.1)	0.45
Antipsychotics	125 (10.1)	53 (10.3)	0.90
Antidepressants	243 (19.6)	109 (21.2)	0.46
Anxiolytics	365 (29.5)	155 (30.2)	0.79

Dichotomous variables reported in absolute numbers and percentages.
Continuous variables reported in medians and IQR.
COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

was typically found to be dispensed for 5 days and the increase in mortality and arrhythmia risks were highest within these first 5 days.[2 9] Still, the absolute excess risk compared with a penicillin V varied and appropriate questions were raised about whether the associations could be generalised to include populations with low baseline risk of cardiovascular disease.[8–10] In a Danish study, by Svanstrøm *et al*, use of clarithromycin was observed to be associated with a significantly increased risk of cardiac death compared with use of penicillin V among Danish adults, 40–74 years of age with no known serious disease.[5] Yet, no increased risk was found for use of roxithromycin nor azithromycin in populations of young and middle-aged adults, 18–70 years of age.[5 8]

The increased risk of cardiovascular death has additionally been found to be higher among adults with a high baseline risk for cardiovascular disease and suggests that pre-existing risk factors play an important role.[2 3 5 8 9] As a consequence, the Food and Drug Administration issued a drug safety communication warning the public that azithromycin could potentially lead to irregular heart rhythm and caution should be shown for individuals at risk for drug-induced ventricular arrhythmias.[4]

Table 2 Characteristics of out-of-hospital cardiac arrest patients in treatment with a specific macrolide ≤7 days before the time of event

	Azithromycin	Clarithromycin	Erythromycin	Roxithromycin	P value*
N (%)	82 (16.0)	88 (17.1)	82 (16.0)	262 (51.0)	
Age, years (IQR)	69.0 (59.6–77.4)	72.1 (64.4–80.4)	68.6 (52.5–77.8)	72.5 (61.4–81.6)	0.03
Male (%)	46 (56.1)	44 (50.0)	37 (45.1)	141 (53.8)	0.46
Income group (%)					
0 (lowest income quintile)	10 (12.2)	8 (9.1)	14 (17.1)	28 (10.7)	
1	21 (25.6)	26 (29.6)	18 (22.0)	66 (25.2)	
2	23 (28.1)	28 (31.8)	27 (32.9)	77 (29.4)	0.15
3	10 (12.2)	13 (14.8)	14 (17.1)	63 (24.1)	
4 (highest income quintile)	18 (22.0)	13 (14.8)	9 (11.0)	28 (10.6)	
Comorbidity (%)					
Diabetes	19 (23.2)	11 (12.5)	11 (13.4)	33 (12.6)	0.11
Peripheral vascular disease	3 (3.7)	3 (3.4)	3 (3.7)	15 (5.7)	0.83
Previous MI	5 (6.1)	13 (14.8)	4 (4.9)	25 (9.5)	0.12
Ischaemic heart disease	8 (9.8)	16 (18.2)	7 (8.5)	30 (11.5)	0.20
Heart failure	13 (15.9)	17 (19.3)	10 (12.2)	30 (11.5)	0.27
Atrial fibrillation	6 (7.3)	8 (9.1)	5 (6.1)	26 (9.9)	0.76
COPD	24 (29.3)	20 (23.6)	15 (18.3)	62 (23.7)	0.43
Cancer	4 (4.9)	11 (12.5)	7 (8.5)	21 (8.0)	0.36
Depression	5 (6.1)	5 (5.7)	1 (1.2)	4 (1.5)	0.04
Any psychiatric disease	13 (15.9)	12 (13.6)	10 (12.2)	22 (8.4)	0.21
Charlson score (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	1 (0–2)	0.16
Concomitant pharmacotherapy (%)					
Lipid-lowering drugs	13 (15.9)	10 (11.4)	9 (11.0)	37 (14.1)	0.74
Loop diuretics	30 (36.6)	34 (38.6)	21 (25.6)	80 (30.5)	0.23
Beta-blockers	17 (20.7)	19 (21.6)	16 (19.5)	45 (16.8)	0.71
ACE inhibitors	22 (26.8)	28 (31.8)	14 (17.1)	58 (22.1)	0.11
Vitamin K antagonists	5 (6.1)	3 (3.4)	2 (2.4)	19 (7.3)	0.33
Antiplatelets	0 (0.0)	1 (1.1)	1 (1.2)	9 (3.4)	0.28
Antipsychotics	12 (14.6)	10 (11.4)	10 (12.2)	21 (8.0)	0.31
Antidepressants	17 (20.7)	20 (22.7)	11 (13.4)	61 (23.3)	0.29
Anxiolytics	22 (26.8)	30 (34.1)	21 (25.6)	82 (31.3)	0.56

Dichotomous variables given in absolute numbers and percentages.
Continuous variables given in medians and IQR.
*P value for differences between roxithromycin, erythromycin, clarithromycin and azithromycin.
COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Overall, the conflicting results between studies on the effects of macrolides underscore the need to clarify the risk associated with macrolides in general. Denmark provides the optimal setting for an investigation, due to the nationwide databases on hospital contacts and prescription of medicine. Our purpose with the retrospective study was therefore to investigate the risk of OHCA in patients prescribed a macrolide (roxithromycin, erythromycin, clarithromycin or azithromycin) using conditional logistic regression in case-crossover analyses with penicillin-V treatment as comparative reference, since penicillin holds similar indications as macrolides, but with no known cardiac risks.[5 11]

METHODS

Study population

All OHCAs in Denmark from 2001 to 2010 that resulted in resuscitative efforts by bystanders (with activation of the emergency medical services (EMS) system) or EMS personnel according to the Danish Cardiac Arrest Register were included in the present study. We included all patients with OHCA who on 1 January 1997 were ≥10

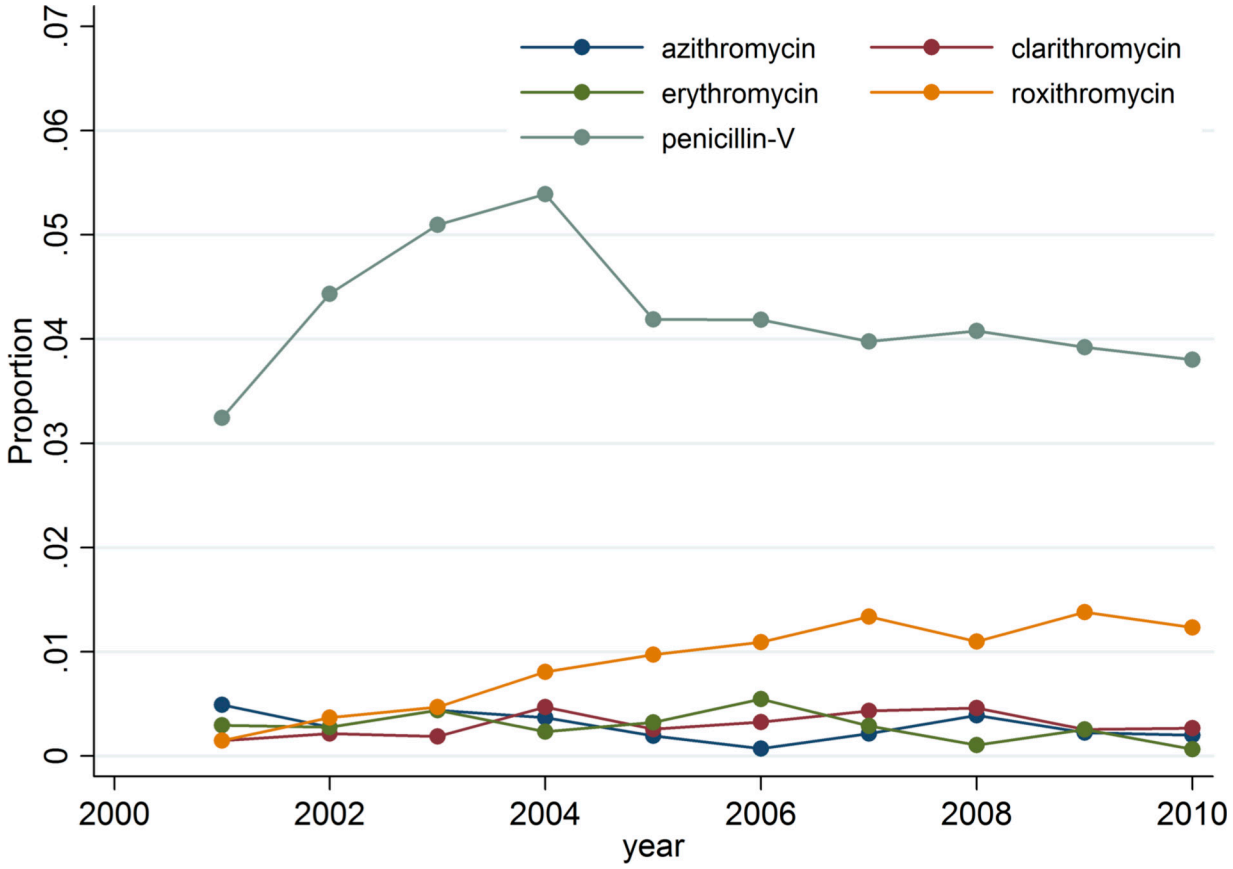

Figure 1 Trends in macrolide and penicillin-V drug usage 7 days before event among individuals who experienced an out-of-hospital cardiac arrest (2001–2010).

years old, as done previously.[12 13] Patients with obvious signs of death (eg, trauma) or patients where no resuscitative efforts were performed by bystanders or EMS personnel were not included in the Danish Cardiac Arrest Registry. Notably, EMS personnel (nationwide) are required to fill out and submit a case report form to the Danish Cardiac Arrest Registry for every OHCA including information on date, time and occurrence of OHCA that ensures a valid and accurate registry.[14]

Databases

All Danish citizens are assigned a unique and permanent civil registration number that enables individual-level-linkage of nationwide registers. For the present study, we used information from the Danish National Patient Registry, the Danish Registry of Medicinal Product Statistics, the National Danish Register of Causes of Death and the Danish Integrated Database for Labour Market Research.

Included in the Danish National Patient Registry is information on every hospital admission and discharge (ie, one primary diagnosis and if appropriate two or more secondary diagnoses) according to the International Classification of Diseases 10th revision (ICD-10).[15]

Since 1995, detailed information on all dispensed drug prescriptions from Danish pharmacies have been registered in the Danish Registry of Medicinal Product Statistics using the Anatomical Therapeutic Chemical (ATC) system.[16] The register is valid and accurate as all Danish pharmacies are obliged by law to register prescriptions due to the partial reimbursement of drug expenses by the government-financed healthcare system.[16]

The National Danish Register of Causes of Death holds information on the primary as well as contributing causes of death.

Patient comorbidity and concomitant pharmacotherapy

Patient comorbidity was defined through the Danish National Patient Registry using primary or secondary hospital discharge diagnoses (up to 5 years before the date of OHCA) for the following diseases specified in the Charlson Comorbidity Index and adapted for use with ICD-10 classification system: atrial fibrillation, cerebral vascular disease, chronic obstructive pulmonary disease, heart failure, ischaemic heart disease, malignancy, myocardial infarction and peripheral vascular disease.[17–19] Diabetes was defined by a redeemed prescription for any glucose-lowering medication (ATC:A10; oral or insulin) ≤180 days before the time of OHCA according to the Danish Register of Medicinal Product Statistics. A history of any psychiatric illness and depression was defined by discharge diagnoses and patients with suicide were defined by primary causes of death. Socioeconomic status was defined by averaging annual income within 5 years.

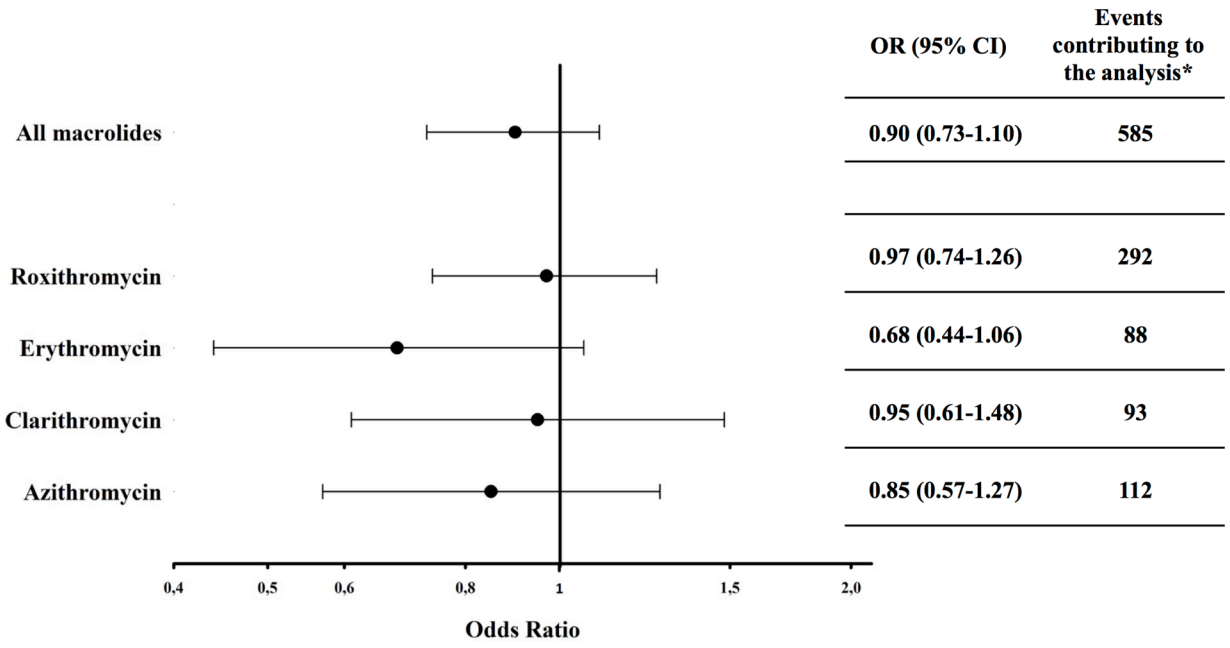

Figure 2 Macrolide treatment and risk of out-of-hospital cardiac arrest using penicillin V as the comparative reference according to the case-crossover analysis. Presented are OR from the conditional logistic regression analysis in case-crossover models (95%CI). *OHCA cases contributing to the analysis were those having a discordant drug exposure history in the case and control periods. OHCA, out-of-hospital cardiac arrest.

Concurrent pharmacotherapy was defined by a claimed prescription ≤90 days before the time of OHCA for the following drugs (ATC-codes): ACE inhibitors (A09A), vitamin K-antagonists (B01AA), antiplatelets (B01AC), loop diuretics (C03C), beta-blockers (C07), cholesterol-lowering agents (C10), sedatives and anxiolytics (N05B and N05C), and antidepressants (N06A).

Antibiotic pharmacotherapy

We identified the most commonly used macrolides and penicillin V among all OHCA cases and age-matched and gender-matched controls from 2001 to 2010 (ATC-code): roxithromycin (J01FA06), erythromycin (J01FA01), clarithromycin (J01FA09), azithromycin (J01FA10) and phenoxymethylpenicillin (J01CE02). For each of the above-mentioned antibiotics, we determined treatment duration by dividing the number of tablets in the prescription of interest with the estimated daily dosage, as defined by current national guidelines.[12 13 20 21]

Statistical analysis

We compared categorical variables for penicillin V and macrolides users with the χ^2 test or Fishers exact where appropriate. Continuous variables were compared with the Kruskall-Wallis test. We used the Cochran-Armitage trend test to evaluate trends in antibiotic treatment.

In our primary analysis, we examined the risk of OHCA associated with specific macrolides using conditional logistic regression in case-crossover analyses and with penicillin-V treatment as comparative references.[22] In brief, the case-crossover design is based on the principles of each individual serving as his or her own control in different time periods. By using each individual as his or her own control, the method is able to adjust for time-invariant confounders including chronic comorbidities (eg, obesity, hypertension and smoking) as well as concomitant pharmacotherapy (eg, statin and beta-blockers) and is suitable for studying transient effects on the risk of acute events.[22]

The case-crossover design only uses patients with discordant exposure histories, so that patients treated in the case period support an OR >1. Conversely, patients treated in the control period support an OR <1. Hence, patients with concordant exposure histories do not contribute to the case-crossover analysis. For the present case-crossover study design, we used one reference period which means that the assumption of conditional independence of exposure at different time-points is not violated.[23–25] We defined the case period as 0–7 days before OHCA and the reference period as 14–21 days before OHCA. A washout period was defined as 7–14 days before OHCA to eliminate possible carry-over effects.

In addition to the case-crossover method, we also performed a secondary analysis using the case–time–control design in order to adjust for time trends in the general prescribing patterns which may otherwise lead to biased results.[23 24] The case–time–control design, extend the case-crossover study design using a control group to account for changes in prescribing patterns not related to the outcome of interest that may otherwise lead to biased results.

For the case–time–control analysis, we used the Danish National Patient Registry, to match each OHCA case with four controls on age and gender using the greedy matching algorithm.[12 13] The control population was

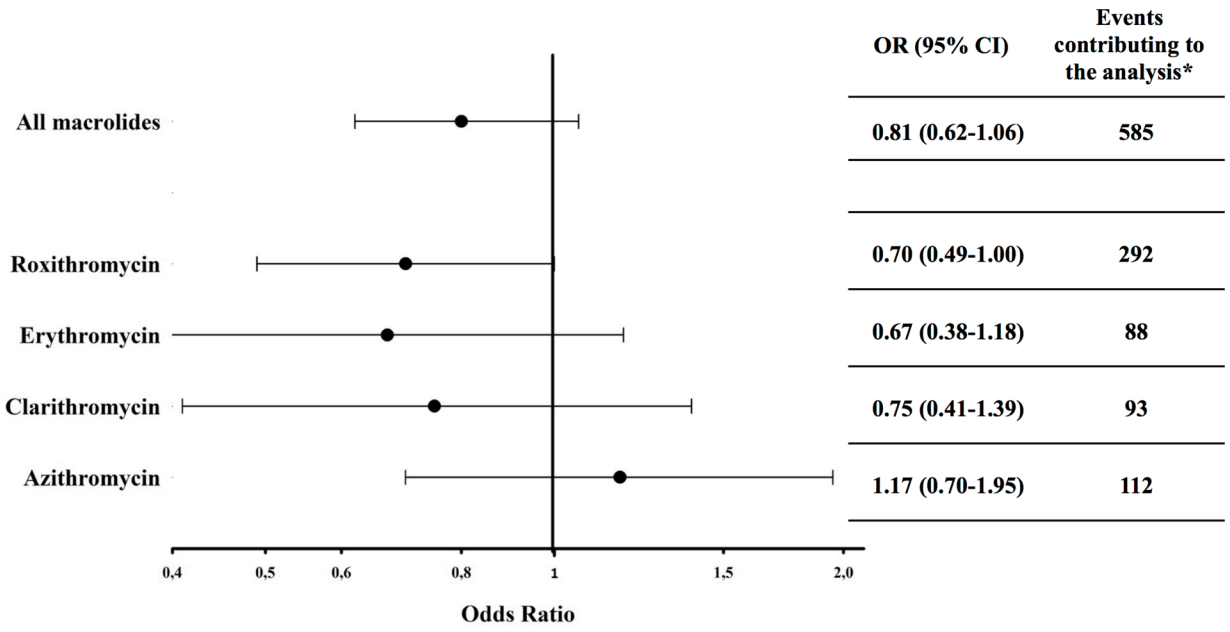

Figure 3 Macrolide treatment and risk of out-of-hospital cardiac arrest using penicillin V as the comparative reference according to the according to case–time–crossover analysis. Presented are OR from the conditional logistic regression analysis in case–time–control models (95%CI). *OHCA cases contributing to the analysis were those having a discordant drug exposure history in the case and control periods. OHCA, out-of-hospital cardiac arrest.

identified in order to account for prescribing changes in the general population.[26] Notably, exposure for each control was determined using the same date of OHCA as the matched case. A two-sided P value <0.05 was considered statistically significant. All analyses were performed using SAS, V.9.4 (SAS Institute).

Other analysis

We tested the robustness of our study findings in multiple sensitivity analyses. While the main case-crossover analysis used 7-day treatment periods, we also performed additional case-crossover and case–time–control analyses with 5, 10, 14 and 21 days treatment periods. In order to eliminate the potential bias introduced by acute deterioration in patient health before OHCA, we repeated our main analysis while excluding patients who had been admitted to hospital 14 days and 365 days before the time of OHCA. Separate analyses excluding patients with a cancer diagnosis ≤5 years before the time of OHCA were also performed. Moreover, we also performed additional analyses where we only included patients with an OHCA of cardiac origin according to the Utstein criteria (definitions of how to report cardiac arrest data).[14] Patients >18 years old and patients with no evidence of substance abuse were also tested separately as were patients with no evidence of attempted suicide.

RESULTS

From 2001 to 2010, we identified a total of 29 111 patients with an OHCA according to the Danish Cardiac Arrest Register. Of these, we identified 514 (0.02%) and 1237 (0.04%) patients in treatment with a macrolide or penicillin V ≤7 days before the time of OHCA, respectively; patient characteristics are listed in table 1. Overall, few differences in patients' characteristics were identified between macrolide or penicillin-V users. Compared with penicillin V, OHCA patients in treatment with a macrolide were less likely to be men (61.8% vs 52.1%, respectively; P<0.001), but more likely to have chronic obstructive pulmonary disease (COPD) (16.3% vs 23.5%, respectively; P<0.001, table 1).

Among 514 patients with OHCA in treatment with a macrolide at the time of OHCA, we identified a total of 262 with roxithromycin (51.0%), 82 with erythromycin (16.0%), 88 with clarithromycin (17.1%) and 82 in treatment with azithromycin (16.0%). Characteristics for patients with OHCA in treatment with a specific macrolide at the time of event are listed in table 2. Although the diagnosis of depression differed according to type of macrolide used (P=0.04), no other significant baseline differences were identified across groups of macrolide users (P>0.05, table 2).

Overall, the use of macrolides 7 days before OHCA increased from 1.1% in 2001 to 1.8% in 2010 (trend; P<0.001) (figure 1). Similarly, macrolide use among the age-matched and gender-matched controls also increased from 0.4% in 2001 to 0.8% in 2010 (trend; P<0.001) (online supplementary figure 1). No significant change in penicillin-V-prescribing patterns among OHCA cases from 2001 to 2010 was identified (3.2% and 3.8%, respectively; trend; P=0.09). Among the age-matched and gender-matched controls, use of penicillin V decreased from 2001 to 2010 (2.1% and 1.5%, respectively; trend; P<0.001) (online supplementary figure 1).

Case-crossover analysis

According to our main case-crossover analysis, risk of OHCA associated with overall macrolide use was comparable with that of penicillin V (OR=0.90; 95% CI 0.73 to 1.10) (figure 2). Similarly, non-different associations with OHCA with specific macrolides compared with penicillin V was identified for: roxithromycin (OR=0.97; 95% CI 0.74 to 1.26), erythromycin (OR=0.68; 95% CI 0.44 to 1.06), clarithromycin (OR=0.95; 95% CI 0.61 to 1.48) and azithromycin (OR=0.85; 95% CI 0.57 to 1.27) (figure 2).

Listed in the online supplementary table 1 are the detailed specifications of exposure to antibiotic treatment by case and control periods. In the online supplementary figure 2 are shown macrolide and penicillin-V treatment and the independent associations with OHCA according to the case-crossover analysis.

Case–time–control analysis

Overall, the case–time–control analyses were in accordance with the results from the main case-crossover analysis (figure 3). Thus, the association suggested lower OR for treatment with overall macrolide use (OR=0.81; 95% CI 0.62 to 1.06) as well as for treatment with specific macrolides (roxithromycin; OR=0.70; 95% CI 0.49 to 1.00), erythromycin (OR=0.67; 95% CI 0.38 to 1.18), clarithromycin (OR=0.75; 95% CI 0.41 to 1.39) or azithromycin (OR=1.17; 95% CI 0.70 to 1.95) (figure 2).

In the online supplementary figure 3, we present macrolide and penicillin-V treatment and the independent risk of OHCA according to the case–time–control analysis.

Sensitivity analysis

Several additional case-crossover and case–time–control analyses were also performed to examine the robustness of our findings. In all instances, the case-crossover and the case–time–control analyses were congruent. First, we excluded patients with a hospital admission 14 days before the time of event that yielded similar estimates as the main case-crossover analysis using penicillin V as the comparative reference (roxithromycin (OR=0.71; 95% CI 0.48 to 1.05), erythromycin (OR=0.75; 95% CI 0.41 to 1.37), clarithromycin (OR=0.77; 95% CI 0.39 to 1.49) and azithromycin (OR=1.11; 95% CI 0.65 to 1.87)).

Similar findings were made when we excluded patients with a hospital admission 365 days before the time of event (data not shown). Second, excluding patients with a non-cardiac aetiology in accordance with the Utstein criteria did also not influence our findings from the case-crossover analysis compared with penicillin V for roxithromycin (OR=1.04; 95% CI 0.75 to 1.46), erythromycin (OR=0.61; 95% CI 0.35 to 1.06), clarithromycin (OR=0.87; 95% CI 0.52 to 1.46) and azithromycin (OR=0.88; 95% CI 0.54 to 1.44).

Third, we excluded patients with cancer, but no change in association was identified (data not shown). Fourth, additional case-crossover and case–time–control analyses with 5, 10, 14 and 21 days treatment periods were performed and did not change the identified associations from the main analysis (data not shown).

We were underpowered to evaluate a clinical meaningful dose–response association between high-dose versus low-dose macrolide and OHCA.

DISCUSSION

In this nationwide study of OHCAs in Denmark, we found that the associated risk of OHCA was comparable between overall and specific macrolide use and use of penicillin V. Furthermore, we found lower ORs for treatment with specific macrolide use (ie, roxithromycin, erythromycin, clarithromycin and azithromycin). Hence, we are not able to show that use of macrolides was independently associated with an increased risk of OHCA when compared with penicillin V. Due to inconsistency between the estimated risks of SCD during macrolide treatment, a question has been raised if the risks previously identified apply to the elderly or patients at risk of cardiovascular disease only. As an example, results from Svanström *et al*, using data from Denmark, found that azithromycin use was not associated with an increased risk of cardiovascular death (mean age, 39.5 to 42 years).[10] These finding disagreed with those by Rao *et al* and Ray *et al*, who investigated somewhat older populations (mean age, 49 and 56.8 years, respectively).[2 9] Despite that our population was somewhat older than the prior studies (71.3 years among macrolide treated patients and 70.8 years among patients treated with penicillin V, table 1), we were not able to specifically link the usage of any macrolides to OHCA compared with use of penicillin V. Our results conflict, in part, with the previously published studies on adverse effects of macrolides; we did not find the past observed increased risks of cardiovascular mortality associated with macrolides and only azithromycin was found to have a higher point estimate compared with penicillin V (online supplementary figure 2).[8 10] Inherent to the statistical study design, we were able to adjust for time-invariant confounders by including chronic comorbidities and concomitant pharmacotherapy in the statistical analyses and also performed additional sensitivity analyses to eliminate bias by acute deterioration in patient health. The majorities of previous studies have been evaluations or examinations of national cohorts with cardiac arrhythmia or mortality as primary outcomes.[2 5 9 10] Nonetheless, Chou *et al* did find a higher risk of cardiac arrhythmia in patients receiving azithromycin compared with patient receiving amoxicillin–clavulanate.[8] However, they also found the risk of cardiovascular mortality to be higher among amoxicillin–clavulanate users than among non-users.[8] This could imply that the risks of OHCA may be due to underlying infection, suggesting that the comparison of antibiotic users and non-users was susceptible to confounding by indication.[8] In Denmark, and as stated by international guidelines, amoxicillin–clavulanate or

ciprofloxacin are used for more severe lower respiratory infections and occasionally as first-line treatment for pneumonia in patients with COPD.[2 27] Hence, it is possible that patients with high-risk comorbidities or more severe infections may be given a broad-spectrum antibiotic and this could bias the estimated risk for OHCA. We found that a significantly higher percentage of patients in the macrolide group were diagnosed with COPD. However, this did not result in an increased OR compared with the penicillin-V group, as previously mentioned, which could have been expected since COPD has been associated with OHCA.[28 29]

In Denmark, the preferred macrolide for respiratory infections is clarithromycin, which we did not find to have stronger association with OHCA than penicillin V. Contrary to the present study, Svanström *et al* found use of clarithromycin to be associated with increased risk of cardiac death.[5] They did, however, find that users of clarithromycin were slightly older and more likely to have a history of respiratory disease. Thus, clarithromycin was likely to have been used for the treatment of asthma and COPD, which is likely to be associated to OHCA with or without antibiotic treatment.[28 29] They did, however, perform a study of a national cohort and they list confounding by indication as a limitation for their study, despite of adjustment by propensity score.[5]

Several limitations apply to the present study. Although, the proarrhythmic properties of macrolide treatment involve prolonged cardiac repolarisation (ie, QT interval prolongation on an ECG) and that a prolonged QT interval may have preceded the OHCA, we are not able to prove such causation given the observational nature of the study. While the present study is the largest study performed to date on macrolide treatment and OHCA risk, the infrequency of OHCA as outcome of this treatment limited the final study cohort and may have influenced our findings. Of note, in neither of the studies, including our own, can we rule out that incorrect diagnosing can lead to OHCA and a misinterpreted association with use of antibiotic. We also acknowledge that patients in whom no resuscitative efforts were performed or patients with obvious signs of death may indeed have suffered from a cardiac arrest, but have been excluded from the Danish Cardiac Arrest Registry. Our current study holds the strength of enrolling members of the general population from a nationwide database containing all patients suffering from an OHCA and data on all patient usage of antibiotics. Unfortunately, data on specific infections, for which the drugs were prescribed, were not available for this study. Yet, we identified 514 and 1237 patients in treatment with a macrolide or penicillin V ≤7 days before the time of OHCA, respectively. Correspondingly, in Denmark, the overall national use of macrolides (combined with lincosamides) and β-lactamase-susceptible penicillins (ie, penicillin V) was approximately 2 DDD/1000 inhabitants vs 4.4 DDD/1000 inhabitants, respectively.[30] Another key strength is the ability to combine the rare outcome OHCA on a national level with information from national registers on hospital admissions, pharmacotherapy and comorbidity.

We speculate if the increased risks previously identified could in fact be related to the severity of infection, the pathogens themselves, comorbidity or incorrect diagnoses and not necessarily the independent use of antibiotics. Yet, while we show no excess risk of OHCA with macrolide use compared with penicillin V, extrapolating these findings to other study populations should be done with caution. However, we do believe that these results can be applied to other similar clinical settings and macrolides can be prescribed when a clear medical indication is present and probable benefit outweighs potential risks, as for other antibiotics.

In conclusion, in this nationwide population-based study, we found comparable magnitude of association between overall and specific macrolide use compared with penicillin V and the risk of OHCA. Notably, the association indicated lower ORs for treatment with specific macrolides suggesting no causal association between OHCA and specific macrolides.

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