RESEARCH

Use of azithromycin and risk of ventricular arrhythmia

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ABSTRACT

BACKGROUND: There are conflicting findings from observational studies of the arrhythrogenic potential of azithromycin. Our aim was to quantify the association between azithromycin use and the risk of ventricular arrhythmia.

METHODS: We conducted a nested case–control study within a cohort of new antibiotic users identified from a network of 7 population-based health care databases in Denmark, Germany, Italy, the Netherlands and the United Kingdom for the period 1997–2010. Up to 100 controls per case were selected and matched by age, sex and database. Recency of antibiotic use and type of drug (azithromycin was the exposure of interest) at the index

date (occurrence of ventricular arrhythmia) were identified. We estimated the odds of ventricular arrhythmia associated with current azithromycin use relative to current amoxicillin use or nonuse of antibiotics (≥ 365 d without antibiotic exposure) using conditional logistic regression, adjusting for confounders.

RESULTS: We identified 14 040 688 new antibiotic users who met the inclusion criteria. Ventricular arrhythmia developed in 12 874, of whom 30 were current azithromycin users. The mean age of the cases and controls was 63 years, and two-thirds were male. In the pooled data analyses across databases, azithromycin use was associated with an increased

risk of ventricular arrhythmia relative to nonuse of antibiotics (adjusted odds ratio [OR] 1.97, 95% confidence interval [CI] 1.35–2.86). This increased risk disappeared when current amoxicillin use was the comparator (adjusted OR 0.90, 95% CI 0.48–1.71). Database-specific estimates and meta-analysis confirmed results from the pooled data analysis.

INTERPRETATION: Current azithromycin use was associated with an increased risk of ventricular arrhythmia when compared with nonuse of antibiotics, but not when compared with current amoxicillin use. The decreased risk with an active comparator suggests significant confounding by indication.

Azithromycin is a widely prescribed broad-spectrum macrolide used mainly for the treatment of respiratory and urinary tract bacterial infections. Concerns have been raised recently regarding its arrhythmogenic potential, a risk already known to be associated with the first marketed macrolide, erythromycin.[1–6] Several case reports have described QT-interval prolongation,[7–9] torsades de pointes[10–12] and polymorphic ventricular tachycardia[13] following use of azithromycin. Many observational studies have reported conflicting results about the association between azithromycin use and cardiovascular death.[14–21] Because the known azithromycin-related cardiac events are related to QT-interval prolongation, torsades de pointes and ventricular arrhythmia,[18,19] these observational studies are limited by the broad category of cardiovascular death used as an outcome, which likely only partially captured cardiac

risk associated with azithromycin use. To date, only 1 observational study has investigated the association between azithromycin use and ventricular arrhythmia specifically.[22]

Given the conflicting findings regarding this widely used antibiotic and the lack of data on ventricular arrhythmia specifically, we aimed to quantify the association between azithromycin use and the risk of ventricular arrhythmia using data from a network of 7 health care databases from 5 European countries.

Methods

Study design and setting

We conducted a nested case–control study within a cohort of new antibiotic users identified from a network of 7 population-based health care databases in 5 European countries that partic-

ipated in the ARITMO (Arrhythmogenic Potential of Drugs) study.[23] The ARITMO study was conducted from Jan. 1, 1997, to Dec. 31, 2010, and the databases covered a total population of about 28 million.

The individual databases were the Health Search Database Cegedim Strategic Data Longitudinal Patient Database (Italy), the Integrated Primary Care Information Database (the Netherlands), The Health Improvement Network (United Kingdom), the PHARMO Database Network (the Netherlands), the Aarhus University Hospital Database (northern and central regions of Denmark), the German Pharmacoepidemiological Research Database (Germany) and the Emilia-Romagna Database (Emiglia-Romagna region of Italy) (Table 1). Harmonized data extraction, quality assurance and analyses when combining multiple health care databases for drug safety studies have been described elsewhere.[24]

The databases in the ARITMO network have been used previously in pharmacoepidemiologic studies,[25] and trends in antibiotic use across databases have been investigated.[26] The ARITMO studies are registered in the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) registry of studies held at the European Medicines Agency (www. encepp.eu/encepp/viewResource.htm?id=4669).

Study population

We included patients 85 years of age or younger who were new antibiotic users (no antibiotic use in the prior year). Cohort entry occurred on the date of the first recorded antibiotic prescription among patients with at least 1 year of database history.

We excluded patients over 85 years of age to avoid immortal time bias. We excluded patients with malignant cancer because they may have been admitted to hospital for long periods, which would preclude full capture of their medical history. In addition, we excluded, wherever possible, people with a record of hospital admission.

We followed patients from the first antibiotic prescription to the earliest of the following: end of study, occurrence of ventricular arrhythmia, transfer out of database, diagnosis of malignant cancer, 85th birthday or death.

Cases and controls

For cases, we identified patients with the primary outcome of ventricular arrhythmia (the case definition and coding algorithms are reported in Appendix 1, eFigure 1 and eTable1, available at www. cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160355/-/DC1). Outcome validation was conducted in every database for a random sample of 200 cases through independent manual review of medical records by 2 experts per database who were blind to drug exposure. In the Integrated Primary Care Information database, manual validation of all automatically detected cases was performed because of extensive use of unstructured, free-text patient notes. A positive predictive value of 90% or higher was achieved.[24] We excluded cases if they were current users of azithromycin and another antibiotic concomitantly; we also excluded cases if they were not current, recent or past users of azithromycin.

We selected up to 100 controls per case and matched them by year of birth (within 1 yr), sex, index date and database using incidence density sampling.

Exposure

We obtained data on antibiotics (Anatomic Therapeutic Chemical classification codes J01*) from the electronic drug prescription/ dispensing records in the study databases. We calculated the

Table1: Features of the databases included in the study

Database	Country	Type of database and setting	Study period	Diagnosis coding	Prescription coding	Source population
AARHUS	Denmark	NHS-linked regional database (northern and central regions); community, and in- and outpatient hospital settings	2000–2010	ICD-10	ATC	1 559 718
ERD	Italy	NHS-linked regional database (Emiglia-Romagna region); community setting	2005–2010	ICD-9-CM	ATC	6 079 798
HSD-CSD-LPD	Italy	Nationwide general practice database; community setting	2000–2010	ICD-9-CM and free text	ATC	1 240 561
GePaRD	Germany	Nationwide general practice database; community and hospital settings	2005–2009	ICD-10-GM	ATC	7 285 935
IPCI	Netherlands	Nationwide general practice database; community setting	1998–2010	ICPC and free text	ATC	1 016 632
PHARMO	Netherlands	Nationwide record linkage system; community setting	1999–2009	ICD-9-CM	ATC	4 625 868
THIN	United Kingdom	Nationwide general practice database; community setting	1997–2010	Read codes and free text	BNF/multilex	6 951 894

Note: AARHUS = Aarhus University Hospital Database; ATC = Anatomic Therapeutic Chemical drug classification; BNF = British National Formulary codes; ERD = Emilia-Romagna Database; GePaRD = German Pharmacoepidemiological Research Database; HSD-CSD-LPD = Health Search Database Cegedim Strategic Data Longitudinal Patient Database; ICD-9-CM = International Classification of Diseases, ninth edition, clinical modification; ICD-10 = International Classification of Diseases, 10th edition; ICD-10-GM = International Classification of Diseases, 10th edition, German modification; ICPC = International Classification of Primary Care; IPCI = Integrated Primary Care Information Database; NHS = National Health Service; THIN = The Health Improvement Network.

exposure period by dividing the total number of units prescribed or dispensed by the daily number of units taken (or the defined daily dose if the prescribed dosage was unavailable).

Exposure to antibiotics was categorized as current, recent or past. Current exposure was defined as the period covering the index date (occurrence of ventricular arrhythmia), or ending within 7 days before the index date to account for lack of compliance with treatment or late registration of ventricular arrhythmia (i.e., to reduce exposure misclassification and outcome misclassification). Recent exposure was defined as the period ending between 7 and 89 days before the index date (complications of severe infections or delayed effects of antibiotic exposure may have an effect on the occurrence of the primary outcome). Past exposure was defined as the period ending between 90 and 364 days before the index date (both antibiotic exposure and infection are likely to have no effect on occurrence of the outcome). To take into account the baseline risk of ventricular arrrhythmia, we defined a non-exposure category as no antibiotic exposure within 365 days before the index date.

Covariates

We considered the following risk factors of ventricular arrhythmia as covariates: age and sex; cardiovascular diseases; metabolic diseases; other diseases potentially related to increased risk of ventricular arrhythmia (e.g., atrial fibrillation or flutter and cardiomyopathies); prior use of anti-arrhythmia drugs, and concomitant use (defined as use within 90 d before index date) of medications known to induce hypokalemia or QT-interval–prolonging drugs (i.e., drugs with established torsadogenic risk according to the CredibleMeds list[27]). (The covariates and coding algorithms are reported in Appendix 1, eTables 2–5, using the harmonization process that has been described before.[24])

Statistical analysis

Data were extracted locally and transformed into a simple common data model according to a process described previously.[28] Data were then transformed locally from the common input files into fully anonymized data sets with use of the custom-built JAVA-based software Jerboa.[29]

We calculated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression analysis for current, recent and past use of azithromycin, with current use of amoxicillin as the primary comparator. We also calculated ORs for current, recent and past use of azithromycin, amoxicillin and other antibiotics using non-exposure to antibiotics as a secondary comparator.

Confounders included in the final models were selected through a stepwise approach. Well-known risk factors for ventricular arrhythmia were included a priori as confounders in the final multivariate model (Appendix 1, eTable 2). Other potential confounders were included if they had a prevalence greater than 5% among the controls and were associated with the outcome in the univariate model. All analyses were conducted in each database, and a meta-analysis of risk estimates from the individual databases was carried out. Heterogeneity across databases was estimated with use of the Cochran Q statistic.

The I^2 statistic was then used to express the percentage variation across the databases due to heterogeneity, with values greater than 75% considered to denote a high level of heterogeneity. As a conservative approach, we used a 2-stage random-effects model for the meta-analysis of pooled data.[30] Only databases with 3 or more cases currently using azithromycin were included in the meta-analysis.

We performed 2 sensitivity analyses. In one, we changed the definition of current antibiotic exposure by excluding the 7-day carry-over period that was used to account for lack of compliance or late registration of ventricular arrhythmia. In another, we excluded all patients who had a diagnosis of acute myocardial infarction reported within 15 days before the index date, to test for confounding owing to recent acute myocardial infarction.

Ethics approval

This study was not conducted with direct patient involvement, and all data were analyzed retrospectively. Prior ethics approval for the study was obtained in line with national regulations.

Results

In the source population of 28 760 406 people, we identified 14 040 688 (48.8%) new antibiotic users who met the inclusion criteria. Ventricular arrhythmia developed in 12 874 (0.1%) and 1 240 431 (8.8%) were selected as matched controls (Figure 1). The mean age of the cases and controls was 63 years, and two-thirds were male (Table 2). Well-known risk factors for ventricular arrhythmia were all more frequent among cases than among controls.

Of the cases, 30 were current azithromycin users, matched to 1344 controls. In the primary analysis, we found no significant increase in risk of ventricular arrhythmia associated with current use of azithromycin versus current use of amoxicillin (adjusted OR 0.94, 95% CI 0.50–1.77) (Table 3). The risk was decreased among recent and past users of azithromycin versus amoxicillin (adjusted OR 0.58, 95% CI 0.38–0.87, and 0.52, 95% CI 0.37–0.73, respectively).

Compared with nonuse of antibiotics, current use of azithromycin was associated with an increased risk of ventricular arrhythmia, which was decreased substantially but remained significant after adjustment for potential confounders (adjusted OR 1.97, 95% CI 1.35–2.86) (Table 4). There was no increased risk of ventricular arrhythmia among recent and past users of azithromycin compared with nonuse of antibiotics (adjusted OR 1.12, 95% CI 0.92–1.37, and 1.10, 95% CI 0.95–1.28, respectively). Use of other antibiotics (excluding azithromycin and amoxicillin) was associated with an increased risk of ventricular arrhythmia compared with nonuse of antibiotics (adjusted OR 1.83, 95% CI 1.71–1.97). An increased risk was also associated with recent and past use of other antibiotics, but the effect was smaller (adjusted OR 1.32, 95% CI 1.25–1.39, for recent use, and 1.11, 95% CI 1.06–1.16, for past use).

For the 2-stage meta-analysis, we used data from only the PHARMO Database Network, the Aarhus University Hospital

Database, the German Pharmacoepidemiological Research Database and the Emilia-Romagna Database, because the other databases had fewer than 3 cases who were current azithromycin users. Heterogeneity among databases was low and nonsignificant (Q statistic 3.39; $p = 0.3$; $I^2 = 11\%$). The comparison of current azithromycin use and current amoxicillin use showed no increased risk of ventricular arrhythmia (OR 1.01, 95% CI 0.38–2.64) (Figure 2). However, the pooled estimate showed an increased risk of ventricular arrhythmia associated with current azithromycin use compared with nonuse of antibiotics (OR 2.44, 95% CI 1.61–3.69) (Figure 3).

The findings were similar to those of the primary analysis when we excluded the 7-day carry-over period: compared with nonuse of antibiotics, current azithromycin use and current amoxicillin use were associated with a similar increased risk of ventricular arrhythmia (adjusted OR 1.9, 95% CI 1.1–3.1, and 1.9, 95% CI 2.5–2.3, respectively). When we excluded patients with a diagnosis of acute myocardial infarction within 15 days before the index date, both azithromycin and amoxicillin use were associated with an increased risk of ventricular arrhythmia compared with nonuse of antibiotics (adjusted OR 1.7, 95% CI 1.2–2.5, and 1.9, 95% CI 1.7–2.2, respectively).

Interpretation

Our study showed an increased risk of ventricular arrhythmia associated with current azithromycin use compared with nonuse of antibiotics. Confounding by indication likely played a major role in the assessment of these associations, because the increased risk disappeared when current amoxicillin use was the comparator. This result was consistent across separate databases as well as in the 1- and 2-stage pooled analyses. Confounding by indication in the context of current azithromycin use versus nonuse of antibiotics refers to the increased baseline risk of ventricular arrhythmia associated with the indication of the antibiotic use (i.e., the infection) rather than the exposure itself (i.e., azithromycin). The comparison between amoxicillin and azithromycin is more likely a true reflection of the risk of ventricular arrhythmia. The rationale behind our use of amoxicillin as a control is therefore twofold: (a) it is not expected to have an increased risk of ventricular arrhythmia; and (b) it would avoid introducing confounding by indication because both amoxicillin and azithromycin have a similar indication of use and spectrum of action. The above is not true of a comparison between azithromycin use and nonuse of antibiotics. Amoxicillin has been used as a comparator in similar studies previously.[14,17]

Given the upper limit of the 95% CI and the crude incidence rate of ventricular arrhythmia in the general population in all 7 databases, we would expect at most 8.07 excess cases of ventricular arrhythmia to be associated with azithromycin use per 100 000 person-years compared with nonuse of antibiotics.

There are conflicting results from large epidemiologic studies reporting the risk of cardiovascular death and, more rarely, cardiac arrhythmia. A US cohort study reported a 2.5- and 2.9-fold increased risk of cardiovascular death compared with amoxicillin and nonuse of antibiotics, respectively, among Medicare beneficiaries.[14] Following publication of these data, the US Food and Drug Administration issued a safety warning about azithromycin-related cardiovascular death.[15] A subsequent Danish study showed that the increased risk of cardiovascular death associated with azithromycin use compared with nonuse of antibiotics (rate ratio 2.85, 95% CI 1.13–7.24) disappeared when use of penicillin V was the comparator (rate ratio 0.93, 95% CI 0.56–1.55).[16] More recently, a cohort study using US Veterans' Affairs data
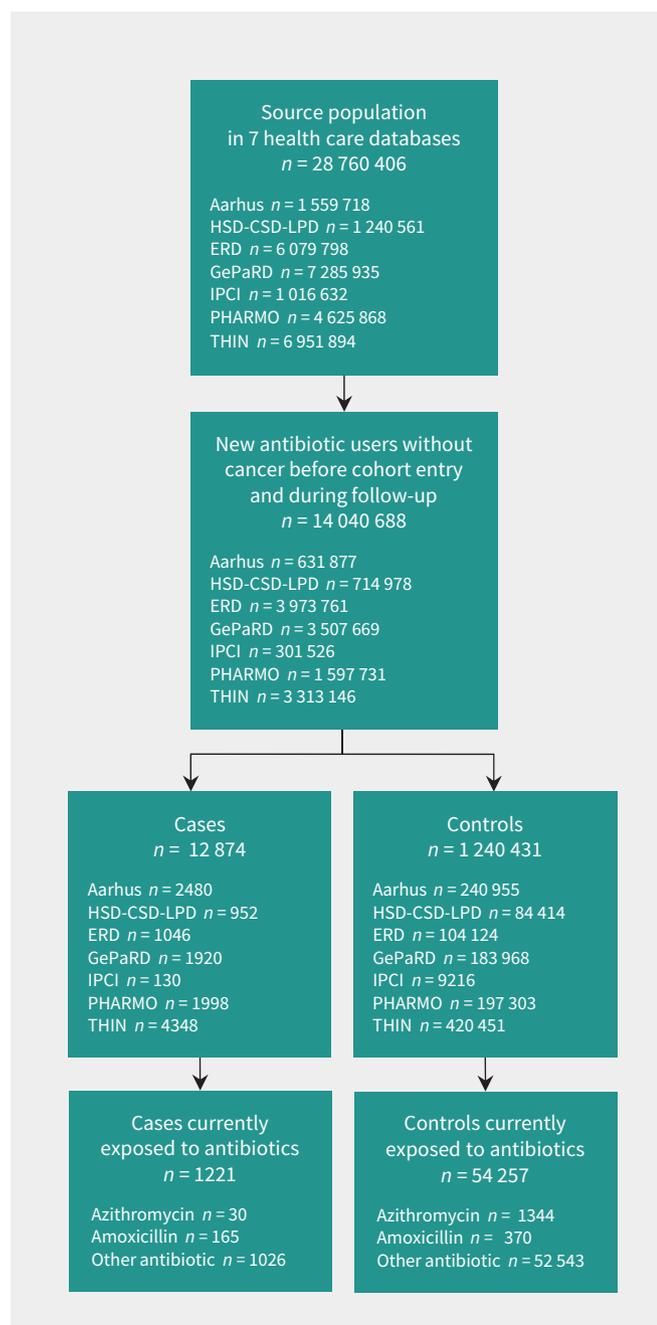

Figure 1: Selection of study cohort from 7 databases. AARHUS = Aarhus University Hospital Database, ERD = Emilia-Romagna Database, GePaRD = German Pharmacoepidemiological Research Database, HSD-CSD-LPD = Health Search Database Cegedim Strategic Data Longitudinal Patient Database, IPCI = Integrated Primary Care Information, PHARMO = PHARMO Database Network, THIN = The Health Improvement Network.

The figure contains the following boxes:

Source population in 7 health care databases
$n = 28\ 760\ 406$

Aarhus $n = 1\ 559\ 718$
HSD-CSD-LPD $n = 1\ 240\ 561$
ERD $n = 6\ 079\ 798$
GePaRD $n = 7\ 285\ 935$
IPCI $n = 1\ 016\ 632$
PHARMO $n = 4\ 625\ 868$
THIN $n = 6\ 951\ 894$

New antibiotic users without cancer before cohort entry and during follow-up
$n = 14\ 040\ 688$

Aarhus $n = 631\ 877$
HSD-CSD-LPD $n = 714\ 978$
ERD $n = 3\ 973\ 761$
GePaRD $n = 3\ 507\ 669$
IPCI $n = 301\ 526$
PHARMO $n = 1\ 597\ 731$
THIN $n = 3\ 313\ 146$

Cases
$n = 12\ 874$

Aarhus $n = 2480$
HSD-CSD-LPD $n = 952$
ERD $n = 1046$
GePaRD $n = 1920$
IPCI $n = 130$
PHARMO $n = 1998$
THIN $n = 4348$

Controls
$n = 1\ 240\ 431$

Aarhus $n = 240\ 955$
HSD-CSD-LPD $n = 84\ 414$
ERD $n = 104\ 124$
GePaRD $n = 183\ 968$
IPCI $n = 9216$
PHARMO $n = 197\ 303$
THIN $n = 420\ 451$

Cases currently exposed to antibiotics
$n = 1221$

Azithromycin $n = 30$
Amoxicillin $n = 165$
Other antibiotic $n = 1026$

Controls currently exposed to antibiotics
$n = 54\ 257$

Azithromycin $n = 1344$
Amoxicillin $n = 370$
Other antibiotic $n = 52\ 543$

Table 2: Demographic and clinical characteristics of ventricular arrhythmia cases and matched controls in an inception cohort of new users of antibiotics across all databases (1-stage pooling)

Characteristic	Group; no. (%) of patients*		
	Cases† n = 12 874	Controls n = 1 240 431	p value
Age, yr, mean ± SD	63.5 ± 15.3	63.6 ± 15.4	Matching factor
Age group, yr			
< 60	4210 (32.7)	405 621 (32.7)	
60–79	7106 (55.2)	678 516 (54.7)	
≥ 80	1558 (12.1)	156 294 (12.6)	
Sex			Matching factor
Male	8561 (66.5)	824 887 (66.5)	
Female	4313 (33.5)	415 544 (33.5)	
Well-known risk factors for ventricular arrhythmia			
Atrial fibrillation/flutter	2332 (18.1)	61 844 (5.0)	< 0.001
Cardiomyopathy	1097 (8.5)	10 887 (0.9)	< 0.001
Cerebrovascular event	1539 (12.0)	81 444 (6.6)	< 0.001
Coronary artery disease	5919 (46.0)	229 811 (18.5)	< 0.001
Electrolyte imbalance	1100 (8.5)	57 663 (4.6)	< 0.001
Heart failure	2913 (22.6)	54 114 (4.4)	< 0.001
Hypertension	10 254 (79.6)	730 389 (58.9)	< 0.001
Peripheral arterial disease	626 (4.9)	26 970 (2.2)	< 0.001
Prior use of anti-arrhythmic drugs	1009 (7.8)	13 865 (1.1)	< 0.001
Concomitant use‡ of medications known to induce hypokalemia	4661 (36.2)	211 284 (17.0)	< 0.001
Concomitant use‡ of QT-interval–prolonging drugs§	2089 (16.2)	75 177 (6.1)	< 0.001
Potential risk factors for ventricular arrhythmia¶			
Alcohol abuse	343 (2.7)	12 157 (1.0)	< 0.001
Chronic liver disease	683 (5.3)	43 325 (3.5)	< 0.001
Chronic respiratory disease	5310 (41.2)	390 364 (31.5)	< 0.001
Conduction disorders	1146 (8.9)	27 911 (2.3)	0.001
Congenital heart disease	151 (1.2)	2968 (0.2)	< 0.001
Diabetes mellitus	2395 (18.6)	140 208 (11.3)	< 0.001
Hyperthyroidism	300 (2.3)	16 195 (1.3)	< 0.001
Hypothyroidism	1033 (8.0)	68 233 (5.5)	< 0.001
Acute and chronic renal failure	802 (6.2)	23 324 (1.9)	< 0.001
Lipid metabolism disorders	5906 (45.9)	351 428 (28.3)	< 0.001
Obesity	1223 (9.5)	71 835 (5.8)	< 0.001
Other cardiac arrhythmias**	1394 (10.8)	34 920 (2.8)	< 0.001
Cardiac valve disorders	1012 (7.9)	28 970 (2.3)	< 0.001

Note: SD = standard deviation.
*Unless stated otherwise.
†Current users of both azithromycin and other antibiotics were not included in the analysis.
‡Within 3 mo before index date.
§Use of drugs with established torsadogenic risk according to CredibleMeds list.[27]
¶Information on smoking status was partly available only in 2 databases and therefore was not included in the final multivariate models.
**Except for atrial fibrillation/flutter, conduction disorders, QT-interval prolongation, ventricular arrhythmia and sudden cardiac death.

reported an almost twofold increased risk of serious arrhythmia associated with current azithromycin use compared with current amoxicillin use.[17]

In 2014, a US study reported that, among older patients admitted to hospital with pneumonia, azithromycin use was associated with a small increased risk of myocardial infarction among azithromycin users compared with nonusers, but no effect on cardiac arrhythmias was observed.[20]

The findings among outpatients from the US studies[14,17,20] conflict with our findings and those reported by Svanström and colleagues.[16] A possible explanation for this is that Medicaid beneficiaries and retired veterans may have a more marked presence of

multiple confounders such as older age, lower socioeconomic status, increased number of comorbidities, obesity, current smoking status and disability, which may make them more vulnerable to the cardiovascular adverse effects of azithromycin than other populations, or increase the impact of residual confounding.

Our findings are in agreement with those from a cohort study involving older patients in Canada (specifically Ontario), which found no increased risk of ventricular arrhythmia associated with macrolide use compared with no macrolide use.[21] The study was based on the assumption that an increased risk of ventricular arrhythmia is a class effect, potentially masking the risk of ventricular arrhythmia associated with individual agents.
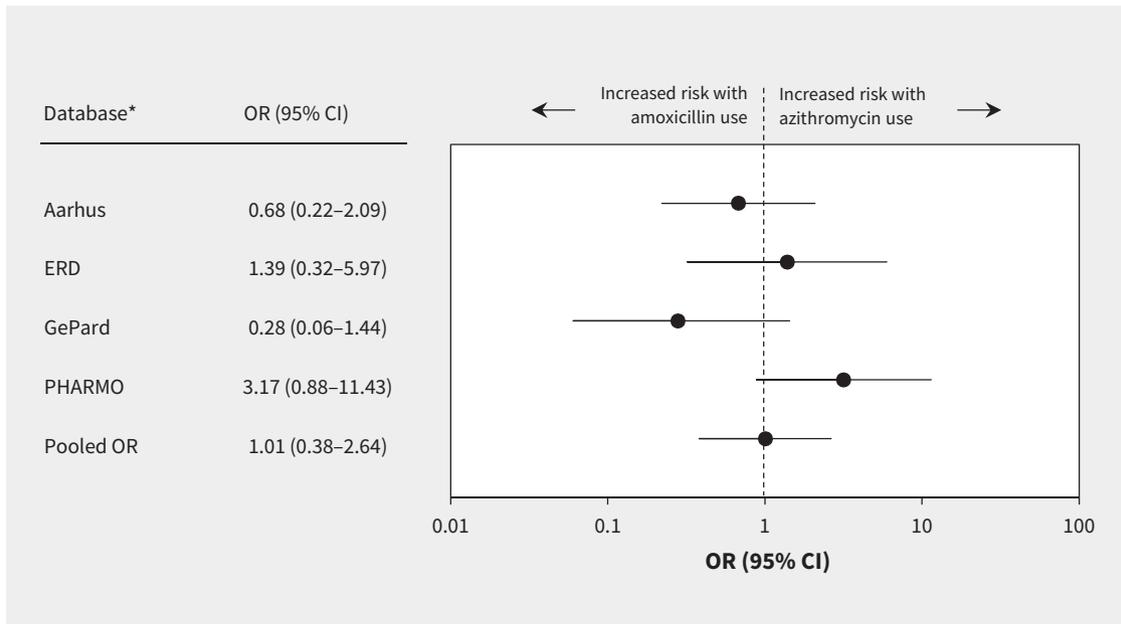
Table 3: Risk of ventricular arrhythmia associated with current, recent and past use of azithromycin compared with current use of amoxicillin (1-stage pooling)

Exposure*	No. (%) of cases† n = 479	No. (%) of controls n = 1848	OR (95% CI)	
			Crude‡	Adjusted§
Current use of amoxicillin	165 (34.4)	370 (20.0)	1.00 (ref)	1.00 (ref)
Use of azithromycin				
Current	30 (6.3)	88 (4.8)	1.05 (0.63–1.74)	0.94 (0.50–1.77)
Recent	107 (22.3)	483 (26.1)	0.60 (0.44–0.83)	0.58 (0.38–0.87)
Past	177 (37.0)	907 (49.1)	0.49 (0.36–0.66)	0.52 (0.37–0.73)

Note: CI = confidence interval, OR = odds ratio, ref = reference category.
*Current = exposure period covered the index date (occurrence of ventricular arrhythmia) or ended within 7 days before the index date; recent = exposure period ended between 7 and 89 days before the index date; past = exposure period ended between 90 and 364 days before the index date.
†Current users of both azithromycin and other antibiotics were not included in the analysis.
‡Crude ORs were estimated for matched case–control pairs and cannot be calculated directly from the values in this table.
§Adjusted for risk factors of ventricular arrhythmia: atrial fibrillation/flutter, cardiomyopathy, coronary artery disease, cerebrovascular disorders, chronic obstructive pulmonary disease, electrolytic imbalance, heart failure, hypertension, diabetes mellitus, lipid disorder, peripheral arterial disease, hypothyroidism, prior use of antiarrhythmic drugs, concomitant use of drugs known to cause hypokalemia, and concomitant use of drugs known to prolong QT interval.

Table 4: Risk of ventricular arrhythmia associated with current, recent and past use of azithromycin and other antibiotics compared with nonuse of antibiotics (1-stage pooling)

Exposure*	No. (%) of cases† n = 12 874	No. (%) of controls n = 1 240 431	OR (95% CI)	
			Crude‡	Adjusted§
Nonuse of antibiotics	5060 (39.3)	601 049 (48.5)	1.00 (ref)	1.00 (ref)
Use of azithromycin				
Current use	30 (0.2)	1344 (0.1)	2.83 (1.97–4.08)	1.97 (1.35–2.86)
Recent use	109 (0.8)	8315 (0.7)	1.65 (1.36–2.00)	1.12 (0.92–1.37)
Past use	187 (1.5)	18 000 (1.5)	1.28 (1.10–1.48)	1.10 (0.95–1.28)
Use of other antibiotics¶				
Current use	1026 (8.0)	52 543 (4.2)	2.43 (2.27–2.60)	1.83 (1.71–1.97)
Recent use	2617 (20.3)	193 154 (15.6)	1.69 (1.61–1.77)	1.32 (1.25–1.39)
Past use	3845 (29.9)	366 026 (29.5)	1.29 (1.23–1.34)	1.11 (1.06–1.16)

Note: CI = confidence interval, OR = odds ratio, ref = reference category.
*Current = exposure period covered the index date (occurrence of ventricular arrhythmia) or ended within 7 days before the index date; recent = exposure period ended between 7 and 89 days before the index date; past = exposure period ended between 90 and 364 days before the index date.
†Current users of both azithromycin and other antibiotics were not included in the analysis.
‡The crude ORs are estimated for matched case-control pairs and cannot be calculated directly from the table above.
§Adjusted for risk factors of ventricular arrhythmia: atrial flutter/fibrillation, cardiomyopathy, coronary artery disease, cerebrovascular disorders, chronic obstructive pulmonary disease, electrolytic imbalance, heart failure, hypertension, diabetes mellitus, lipid disorders, peripheral arterial disease, hypothyroidism, prior use of antiarrhythmic drugs, concomitant use of drugs known to cause hypokalemia, and concomitant use of drugs known to prolong QT interval.
¶Does not include amoxicillin.

That the risk of ventricular arrhythmia for macrolides as a class does not necessarily reflect the risk of individual macrolide antibiotics was illustrated by Chou and colleagues,[22] who conducted the only published cohort study to date investigating the association between ventricular arrhythmia and azithromycin use, set in the Taiwan National Health Insurance Database. Electrophysiologic evidence supports our findings and suggests that azithromycin lacks arrhythmogenic potential at therapeutic doses.[31,32] Fever itself may be a risk factor for arrhythmia, and therefore confounding by indication is pronounced when antibiotics are used in patients with high fever.[33]

Strengths and limitations
Main strengths of our study include the size of the database network used, since ventricular arrhythmia is a rare outcome, and the common methodology used. All of the databases except the

Database*	OR (95% CI)
Aarhus	0.68 (0.22–2.09)
ERD	1.39 (0.32–5.97)
GePard	0.28 (0.06–1.44)
PHARMO	3.17 (0.88–11.43)
Pooled OR	1.01 (0.38–2.64)

Figure 2: Database-specific risk of ventricular arrhythmia associated with current use of azithromycin compared with current use of amoxicillin (2-stage random-effects model). Values greater than 1.0 indicate an increased risk of ventricular arrhythmia with use of azithromycin (values plotted on logarithmic scale). Cochran Q = 0.08; p = 0.1; I^2 = 51%. CI = confidence interval, OR = odds ratio. *Databases with fewer than 3 exposed cases were not included in the model.

Database *	OR (95% CI)
Aarhus	2.17 (1.09–4.31)
ERD	2.26 (1.04–4.90)
Gepard	1.36 (0.49–3.73)
PHARMO	4.10 (1.98–8.48)
Pooled OR	2.44 (1.61–3.69)
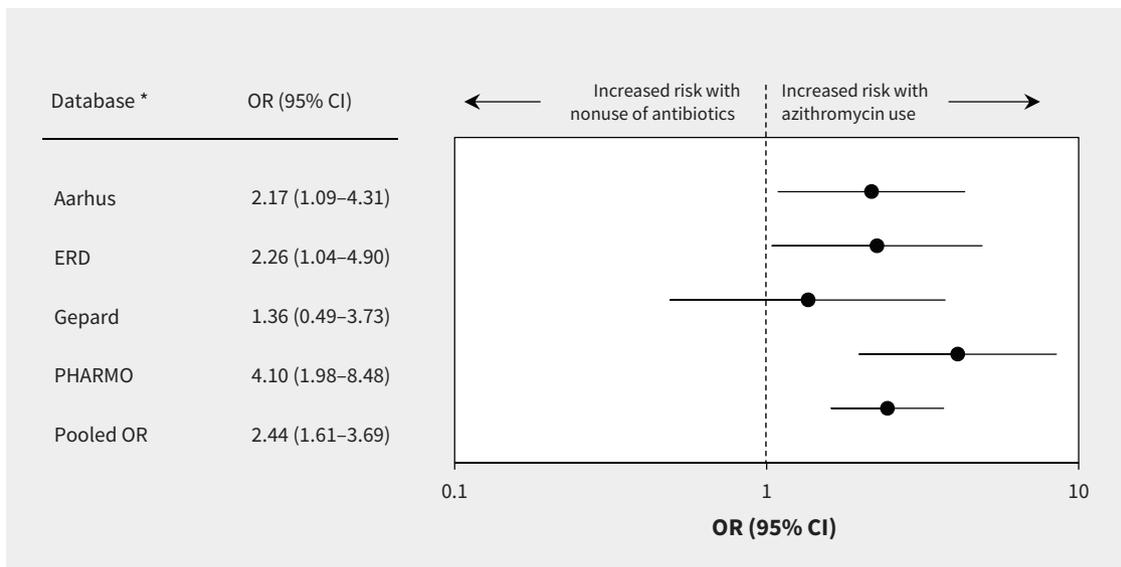
Figure 3: Database-specific risk of ventricular arrhythmia associated with current use of azithromycin versus nonuse of antibiotics (2-stage random-effects model). Values greater than 1.0 indicate an increased risk of ventricular arrhythmia with use of azithromycin (values plotted on logarithmic scale). Cochran Q = 3.4; p = 0.3; I^2 = 11.4%. CI = confidence interval, OR = odds ratio. *Databases with fewer than 3 exposed cases were not included in the model.

Emiglia-Romagna Database and the Aarhus University Hospital Database are representative of the countries from which data were drawn. In addition, exposure to individual antibiotics was identified in such a way that only users of a single antibiotic were included in the analyses.

Results from the 1-stage pooling were confirmed in the meta-analysis (2-stage pooling) of risk estimates from the individual databases. Taken together, these factors substantially increase the reliability of the study findings. Although it may be considered a limitation that 3 of the databases were excluded from the 2-stage pooling analysis owing to the low number of cases, all 7 databases were included in the 1-stage pooling analysis.

Our study has some other limitations. Exposure misclassification was possible if patients did not fill their prescriptions or take their medications. However, risk estimates were consistent across databases, which suggests a negligible effect of this bias. In addition, exclusion of the 7-day carry-over period to take into account lack of compliance yielded results similar to those of the primary analysis.

The exclusion of cancer patients and those 85 years and older may be considered a limitation; however, the latter approach has been used previously.[34,35]

Findings from our study may not be directly extrapolated to the hospital setting, because the health status of patients and the nature of antibiotic use in the community setting is likely to be very different.

Conclusion

In this large population-based study of data from 7 European countries, current azithromycin use was associated with an increased risk of ventricular arrhythmia when compared with nonuse of antibiotics, but not when compared with current amoxicillin use. The decreased risk with an active comparator suggests significant confounding by indication.

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