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RESEARCH

Cardiovascular Toxicity Profile of Macrolides Investigated Using VigiBase Data: A Pharmacovigilance Study

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Abstract

Macrolides are associated with cardiovascular toxicity risk. However, data on their cardiovascular toxicity profiles beyond QT prolongation are limited, and differences in the profiles among various macrolide antibiotics remain unclear. We investigated the cardiovascular toxicity profiles of different macrolides using VigiBase, a global database of individual case-safety reports. Disproportionality analysis was performed using VigiBase, the WHO Pharmacovigilance database, from 1968 to December 2023. Associations between five macrolides (erythromycin, clarithromycin, azithromycin, josamycin, and roxithromycin) and adverse events (20 cardiovascular toxicities and diarrhea as a positive control) were predicted using the reporting odds ratio. Reported outcomes were evaluated for suggested drug-adverse event associations. Among the 36,129,107 reports analyzed, azithromycin was the most commonly used macrolide, followed by erythromycin, clarithromycin, roxithromycin, and josamycin. Diarrhea was frequently reported among users. Azithromycin use was associated with hypertension, cardiac valve disorders, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, torsade de pointes/QT prolongation, cardiac conduction disorders, heart failure, and hemorrhage-related laboratory abnormalities. Erythromycin and clarithromycin use were also associated with cardiac valve disorders, ventricular tachyarrhythmias, torsade de pointes/QT prolongation, and cardiac conduction disorders. The rates of caused/prolonged hospitalization in azithromycin-related hypertension, heart failure, and bleeding-related laboratory abnormality were 46%, 45%, and 50%, respectively. Each of the macrolide antimicrobials was associated with various cardiovascular toxicities, including Cardiac valve disorder, shock, and QT prolongation. Notably, azithromycin was associated with an increased frequency of reported hypertension and heart failure, distinguishing it from the other drugs. These results highlight the importance of considering the cardiovascular toxicity profile of individual macrolide antibiotics when prescribing them.

Keywords Cardiovascular toxicity · Hypertension · Macrolide · Vigibase

Introduction

Macrolides are among the most frequently prescribed antimicrobial agents. However, they are associated with an increased risk of cardiovascular toxicity [1–4]. Specifically, their effects on cardiac repolarization represent a major

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concern, potentially leading to arrhythmias. Therefore, the United States has warned against the use of azithromycin and clarithromycin in adults at high risk of cardiovascular complications [5, 6]. Erythromycin and clarithromycin can cause concentration-dependent bradycardia in rat embryonic hearts and early afterdepolarizations (EADs) and torsade de pointes (TdP) in rabbit hearts, particularly under low potassium levels [7, 8]. Notably, although azithromycin induces QT interval prolongation, it does not induce EADs or TdP, suggesting a lower proarrhythmic potential than that induced by erythromycin and clarithromycin [8]. This disparity may be associated with the distinct patterns of action potential prolongation induced by these drugs [9]. Moreover, a meta-analysis revealed a lower risk of myocardial infarction with azithromycin than with either clarithromycin or erythromycin [10]. Therefore, the cardiovascular toxicity profile of macrolide antibiotics may differ among different agents; however, the specific differences in these profiles remain unclear. Additionally, the associations between each macrolide antimicrobial and various cardiovascular toxicities, as well as the extent and characteristics of cardiovascular toxicity in real-world populations, remain unknown.

Understanding the cardiovascular toxicity profiles of various macrolide antimicrobials is crucial to developing appropriate monitoring strategies for patients with various cardiovascular risk factors. Therefore, in the present study, we aimed to evaluate the cardiovascular toxicity profiles of macrolide antimicrobial agents using VigiBase, a large-scale pharmacovigilance database.

Methods

Pharmacovigilance Analysis

VigiBase is the largest global reporting database for medicinal products maintained by the Uppsala Monitoring Center in Sweden, with over 30 million adverse event reports collected since 1968 (Uppsala Monitoring Centre, VigiBase). Data since the inception of VigiBase to December 2023 were used in this study. As VigiBase contains duplicate reports, we excluded duplicate reports using statistical algorithms developed by the Uppsala Monitoring Center. The downloaded data were processed using the SQLite database (version 3.33.0; SQLite Consortium, Charlotte, NC, USA). This study was approved by the Ethics Committee of Tokushima University Hospital (approval number: 4492).

The association of five macrolide antibiotics—azithromycin, erythromycin, clarithromycin, josamycin, and roxithromycin—with various cardiovascular toxicities was investigated. The definitions of adverse events in this study adhered to those in the Medical Dictionary for Regulatory Activities (MedDRA), which was developed by the International

Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH, MedDRA). Twenty cardiovascular toxicities were investigated, as described previously [11, 12]. The reported odds ratios (RORs) for diarrhea, a common adverse event associated with macrolides, were also calculated for reference. The adverse events are listed in Online Resource 1.

Statistical Analysis

Categorical variables are expressed as frequency and percentage, and basic demographic characteristics were compared using the chi-squared test. Statistical significance was set at $p < 0.05$. RORs were used to assess signal detection, with a signal considered detected when the lower limit of the 95% confidence interval (CI) of the ROR was > 1 [13]. ROR is defined as the odds ratio of the drug of interest in relation to a specific adverse event report. Adverse event reports were divided into four groups: (a) those reporting the adverse drug reaction (ADR) of the drug of interest, (b) those not reporting the ADR of the drug of interest, (c) those reporting the ADR of all other drugs, and (d) those not reporting the ADR of all other drugs. The ROR was calculated as follows:

$$ROR = (a/b)/(c/d).$$

For macrolide-adverse event pairs with a detected safety signal, the proportion of patient outcomes was evaluated. These outcomes were evaluated in six categories—"Caused/Prolonged Hospitalization," "Congenital anomaly/Birth defect," "Death," "Disabling/Incapacitating," "Life-threatening," and "Other"—and missing values were excluded. These analyses were performed using R statistical software (version 4.0.3; R Foundation, Vienna, Austria) [14].

Results

The characteristics of patients are presented in Table 1. A total of 36,129,107 reports were analyzed. The proportion of macrolide users aged 45–64 years was the highest among all age groups. There were more female patients using macrolides than male patients in the dataset (Table 1). Azithromycin was the most commonly used macrolide, followed by clarithromycin and erythromycin. Initially, we examined diarrhea, a common adverse event associated with macrolide use, and found it to be significantly more frequently reported among patients using macrolide antimicrobial agents. Moreover, we analyzed the frequency of cardiovascular toxicities associated with each macrolide using all reported cases. The results indicated that azithromycin use was associated with hypertension (ROR, 1.1; 95% CI, 1.02–1.12; Fig. 1).

Table 1 Patient characteristics

	Azithromycin	Clarithromycin	Erythromycin	Josamycin	Roxithromycin
n	140,664	81,790	59,563	1619	17,830
Age (%)					
0–27 days	200 (0.1)	213 (0.3)	191 (0.3)	11 (0.7)	39 (0.2)
28 days to 23 months	2967 (2.1)	1361 (1.7)	3032 (5.1)	83 (5.1)	87 (0.5)
2–11 years	13,612 (9.7)	4883 (6.0)	7154 (12.0)	341 (21.1)	1081 (6.1)
12–17 years	4671 (3.3)	2149 (2.6)	2887 (4.8)	97 (6.0)	700 (3.9)
18–44 years	36,561 (26.0)	20,605 (25.2)	16,818 (28.2)	472 (29.2)	6259 (35.1)
45–64 years	31,156 (22.1)	20,274 (24.8)	11,134 (18.7)	256 (15.8)	4945 (27.7)
65–74 years	14,338 (10.2)	10,552 (12.9)	5118 (8.6)	130 (8.0)	2074 (11.6)
> =75 years	10,777 (7.7)	9470 (11.6)	4000 (6.7)	117 (7.2)	1654 (9.3)
Unknown	26,382 (18.8)	12,283 (15.0)	9229 (15.5)	112 (6.9)	991 (5.6)
Sex (%)					
Female	77,586 (55.2)	47,316 (57.9)	35,000 (58.8)	969 (59.9)	10,408 (58.4)
Male	56,513 (40.2)	30,290 (37.0)	21,760 (36.5)	637 (39.3)	7192 (40.3)
Unknown	6565 (4.7)	4184 (5.1)	2803 (4.7)	13 (0.8)	230 (1.3)
Report Year (%)					
1968	0 (0.0)	0 (0.0)	24 (0.0)	0 (0.0)	0 (0.0)
1969	0 (0.0)	0 (0.0)	90 (0.2)	0 (0.0)	0 (0.0)
1970	0 (0.0)	0 (0.0)	69 (0.1)	0 (0.0)	0 (0.0)
1971	0 (0.0)	0 (0.0)	97 (0.2)	0 (0.0)	0 (0.0)
1972	0 (0.0)	0 (0.0)	135 (0.2)	0 (0.0)	0 (0.0)
1973	0 (0.0)	0 (0.0)	225 (0.4)	1 (0.1)	0 (0.0)
1974	0 (0.0)	0 (0.0)	138 (0.2)	3 (0.2)	0 (0.0)
1975	0 (0.0)	0 (0.0)	164 (0.3)	0 (0.0)	0 (0.0)
1976	0 (0.0)	0 (0.0)	155 (0.3)	0 (0.0)	0 (0.0)
1977	0 (0.0)	0 (0.0)	193 (0.3)	2 (0.1)	0 (0.0)
1978	0 (0.0)	0 (0.0)	168 (0.3)	1 (0.1)	0 (0.0)
1979	0 (0.0)	0 (0.0)	277 (0.5)	1 (0.1)	0 (0.0)
1980	0 (0.0)	0 (0.0)	317 (0.5)	0 (0.0)	0 (0.0)
1981	0 (0.0)	0 (0.0)	329 (0.6)	7 (0.4)	0 (0.0)
1982	0 (0.0)	0 (0.0)	400 (0.7)	8 (0.5)	0 (0.0)
1983	0 (0.0)	0 (0.0)	883 (1.5)	2 (0.1)	0 (0.0)
1984	0 (0.0)	0 (0.0)	582 (1.0)	0 (0.0)	0 (0.0)
1985	0 (0.0)	0 (0.0)	693 (1.2)	4 (0.2)	0 (0.0)
1986	0 (0.0)	0 (0.0)	854 (1.4)	7 (0.4)	0 (0.0)
1987	0 (0.0)	0 (0.0)	616 (1.0)	45 (2.8)	0 (0.0)
1988	0 (0.0)	0 (0.0)	1479 (2.5)	55 (3.4)	0 (0.0)
1989	1 (0.0)	0 (0.0)	1456 (2.4)	47 (2.9)	51 (0.3)
1990	9 (0.0)	0 (0.0)	1011 (1.7)	51 (3.2)	58 (0.3)
1991	5 (0.0)	3 (0.0)	1144 (1.9)	23 (1.4)	73 (0.4)
1992	40 (0.0)	757 (0.9)	1119 (1.9)	63 (3.9)	666 (3.7)
1993	158 (0.1)	1090 (1.3)	861 (1.4)	38 (2.3)	274 (1.5)
1994	325 (0.2)	1939 (2.4)	1961 (3.3)	83 (5.1)	364 (2.0)
1995	217 (0.2)	1695 (2.1)	1136 (1.9)	33 (2.0)	437 (2.5)
1996	308 (0.2)	1249 (1.5)	823 (1.4)	50 (3.1)	336 (1.9)
1997	630 (0.4)	1495 (1.8)	795 (1.3)	53 (3.3)	283 (1.6)
1998	271 (0.2)	712 (0.9)	567 (1.0)	49 (3.0)	252 (1.4)
1999	602 (0.4)	1064 (1.3)	645 (1.1)	20 (1.2)	172 (1.0)
2000	4445 (3.2)	2399 (2.9)	916 (1.5)	27 (1.7)	207 (1.2)
2001	1525 (1.1)	898 (1.1)	789 (1.3)	22 (1.4)	228 (1.3)

Table 1 (continued)

	Azithromycin	Clarithromycin	Erythromycin	Josamycin	Roxithromycin
2002	476 (0.3)	602 (0.7)	490 (0.8)	8 (0.5)	200 (1.1)
2003	695 (0.5)	747 (0.9)	527 (0.9)	3 (0.2)	153 (0.9)
2004	736 (0.5)	797 (1.0)	886 (1.5)	3 (0.2)	224 (1.3)
2005	1236 (0.9)	1043 (1.3)	767 (1.3)	43 (2.7)	388 (2.2)
2006	1161 (0.8)	939 (1.1)	681 (1.1)	63 (3.9)	330 (1.9)
2007	170 (0.1)	164 (0.2)	94 (0.2)	1 (0.1)	49 (0.3)
2008	2040 (1.5)	1800 (2.2)	1173 (2.0)	45 (2.8)	206 (1.2)
2009	1683 (1.2)	1745 (2.1)	1415 (2.4)	8 (0.5)	682 (3.8)
2010	2096 (1.5)	2352 (2.9)	1305 (2.2)	16 (1.0)	276 (1.5)
2011	4469 (3.2)	3594 (4.4)	2625 (4.4)	57 (3.5)	1042 (5.8)
2012	2952 (2.1)	2431 (3.0)	1356 (2.3)	9 (0.6)	467 (2.6)
2013	2406 (1.7)	3005 (3.7)	1122 (1.9)	13 (0.8)	182 (1.0)
2014	9150 (6.5)	4607 (5.6)	2606 (4.4)	220 (13.6)	1135 (6.4)
2015	9065 (6.4)	4637 (5.7)	2404 (4.0)	48 (3.0)	1036 (5.8)
2016	8892 (6.3)	5396 (6.6)	2413 (4.1)	46 (2.8)	1532 (8.6)
2017	9518 (6.8)	5527 (6.8)	2576 (4.3)	47 (2.9)	1037 (5.8)
2018	10,489 (7.5)	5872 (7.2)	2581 (4.3)	77 (4.8)	835 (4.7)
2019	14,956 (10.6)	6322 (7.7)	4126 (6.9)	65 (4.0)	1154 (6.5)
2020	19,572 (13.9)	5056 (6.2)	2978 (5.0)	50 (3.1)	1856 (10.4)
2021	12,325 (8.8)	4052 (5.0)	2698 (4.5)	36 (2.2)	744 (4.2)
2022	9343 (6.6)	3470 (4.2)	1934 (3.2)	39 (2.4)	255 (1.4)
2023	8698 (6.2)	4331 (5.3)	1695 (2.8)	27 (1.7)	646 (3.6)
Report Region (%)					
African Region	1183 (0.8)	297 (0.4)	994 (1.7)	0 (0.0)	11 (0.1)
Eastern Mediterranean Region	2915 (2.1)	742 (0.9)	551 (0.9)	31 (1.9)	56 (0.3)
European Region	21,569 (15.3)	31,222 (38.2)	17,036 (28.6)	1445 (89.3)	4814 (27.0)
Region of the Americas	66,006 (46.9)	23,731 (29.0)	21,898 (36.8)	7 (0.4)	62 (0.3)
South-East Asia Region	9968 (7.1)	2335 (2.9)	2751 (4.6)	0 (0.0)	3476 (19.5)
Unknown	39,023 (27.7)	23,463 (28.7)	16,333 (27.4)	136 (8.4)	9411 (52.8)
Report Type (%)					
Other	1088 (0.8)	640 (0.8)	127 (0.2)	2 (0.1)	20 (0.1)
PMS/Special monitoring	229 (0.2)	1247 (1.5)	556 (0.9)	39 (2.4)	869 (4.9)
Report from study	11,832 (8.4)	5046 (6.2)	2063 (3.5)	25 (1.5)	924 (5.2)
Spontaneo us	97,939 (69.6)	70,459 (86.1)	51,871 (87.1)	1480 (91.4)	11,713 (65.7)
Not available to sender (unknown)	273 (0.2)	690 (0.8)	69 (0.1)	1 (0.1)	118 (0.7)
Unknown	29,303 (20.8)	3708 (4.5)	4877 (8.2)	72 (4.4)	4186 (23.5)
Outcome (%)	94,814 (67.4)	62,430 (76.3)	51,025 (85.7)	1325 (81.8)	16,459 (92.3)
Caused/Prolonged Hospitalization	18,926 (13.5)	7438 (9.1)	3096 (5.2)	191 (11.8)	826 (4.6)
Congenital anomaly/Birth defect	191 (0.1)	38 (0.0)	46 (0.1)	1 (0.1)	6 (0.0)
Death	4788 (3.4)	1427 (1.7)	743 (1.2)	5 (0.3)	95 (0.5)
Disabling/Incapacitating	935 (0.7)	732 (0.9)	289 (0.5)	2 (0.1)	38 (0.2)
Life threatening	2531 (1.8)	1338 (1.6)	596 (1.0)	18 (1.1)	100 (0.6)
Other	18,479 (13.1)	8387 (10.3)	3768 (6.3)	77 (4.8)	306 (1.7)
Unknown	94,814 (67.4)	62,430 (76.3)	51,025 (85.7)	1325 (81.8)	16,459 (92.3)
Report Source (%)					
Consumer or other non-health professional	21,741 (15.5)	9744 (11.9)	5073 (8.5)	111 (6.9)	538 (3.0)
Lawyer	3066 (2.2)	314 (0.4)	318 (0.5)	0 (0.0)	11 (0.1)
Other Health Professional	20,149 (14.3)	9356 (11.4)	4048 (6.8)	24 (1.5)	485 (2.7)
Pharmacist	16,175 (11.5)	11,524 (14.1)	4185 (7.0)	125 (7.7)	2315 (13.0)
Physician	38,059 (27.1)	33,609 (41.1)	27,693 (46.5)	1215 (75.0)	7870 (44.1)

Table 1 (continued)

|	Azithromycin	Clarithromycin	Erythromycin	Josamycin	Roxithromycin
Unknown	41,474 (29.5)	17,243 (21.1)	18,246 (30.6)	144 (8.9)	6611 (37.1)
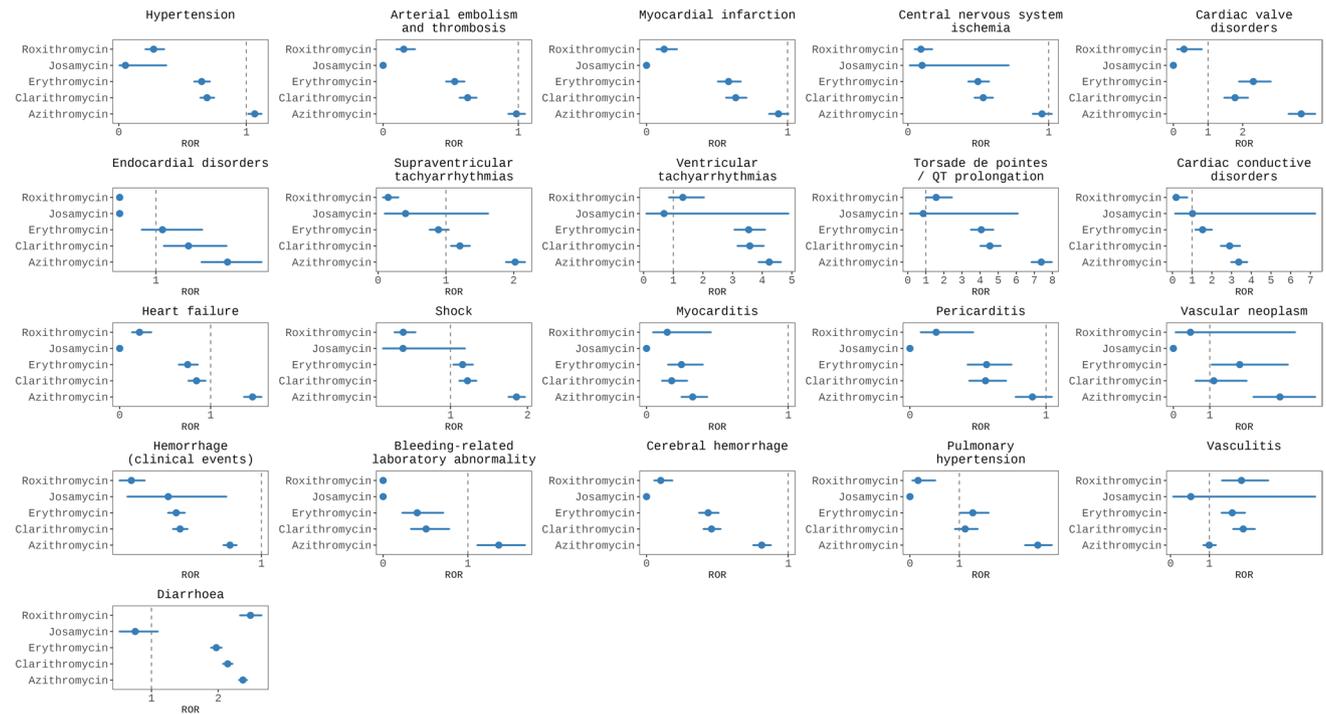
Fig. 1 Disproportionality analysis for all data. The forest plot presents the reporting odds ratios (ROR) with 95% confidence intervals for each cardiovascular adverse event

The use of azithromycin (ROR, 3.7; 95% CI, 3.33–4.09), erythromycin (ROR, 2.3; 95% CI, 1.90–2.80), and clarithromycin (ROR, 1.8; 95% CI, 1.47–2.15) was associated with cardiac valve disorder. Azithromycin (ROR, 2.0; 95% CI, 1.89–2.16) and clarithromycin (ROR, 1.2; 95% CI 1.08–1.35) uses were associated with supraventricular tachyarrhythmias. Azithromycin (ROR, 4.2; 95% CI, 3.88–4.62), erythromycin (ROR, 3.5; 95% CI, 3.07–4.09), and clarithromycin (ROR, 3.6; 95% CI, 3.17–4.05) uses were associated with ventricular tachyarrhythmias. The use of azithromycin (ROR, 7.4; 95% CI, 6.85–7.96), erythromycin (ROR, 4.1; 95% CI, 3.50–4.72), clarithromycin (ROR, 4.5; 95% CI, 4.03–5.13), or roxithromycin (ROR, 1.6; 95% CI, 1.01–2.43) was associated with TdP/QT prolongation. We observed an association between cardiac conduction disorders and azithromycin (ROR, 3.4; 95% CI, 2.99–3.79), erythromycin (ROR, 1.5; 95% CI, 1.17–1.99), and clarithromycin (ROR, 2.9; 95% CI 2.46–3.42) use. Azithromycin use was associated with heart failure (ROR, 1.46; 95% CI, 1.37–1.56) and hemorrhage-related laboratory abnormalities (ROR, 1.4; 95% CI, 1.11–1.67). Roxithromycin exhibited safety

signals associated with torsade de pointes (ROR 1.57, 95% CI 1.01–2.43), vasculitis (ROR 1.83, 95% CI 1.33–2.51), and diarrhea (ROR 2.48, 95% CI 2.33–2.65). Josamycin did not demonstrate any safety signals for any of the cardiovascular adverse events analyzed in this study.

We observed a tendency for signal differences in arterial embolism and thrombosis, myocardial infarction, and central nervous system ischemia after azithromycin treatment between male and female patients (Figs. 2 and 3). We also observed a higher ROR for arterial embolism and thrombosis, myocardial infarction, and central nervous system ischemia among female patients than among male patients (ROR: 1.3, 95% CI: 1.15–1.37 vs. ROR: 2.4, 95% CI: 2.21–2.60; ROR: 1.2, 95% CI: 1.04–1.28 vs. ROR: 2.4, 95% CI: 2.21–2.60; ROR: 1.2, 95% CI: 1.10–1.32 vs. ROR: 2.4, 95% CI: 2.21–2.60, respectively).

The patient outcome "caused/prolonged hospitalization" for TdP/QT prolongation associated with azithromycin, erythromycin, and clarithromycin was 28%, 28%, and 33%, respectively (Fig. 4). The rates of caused/prolonged hospitalization in azithromycin-related hypertension, heart failure,
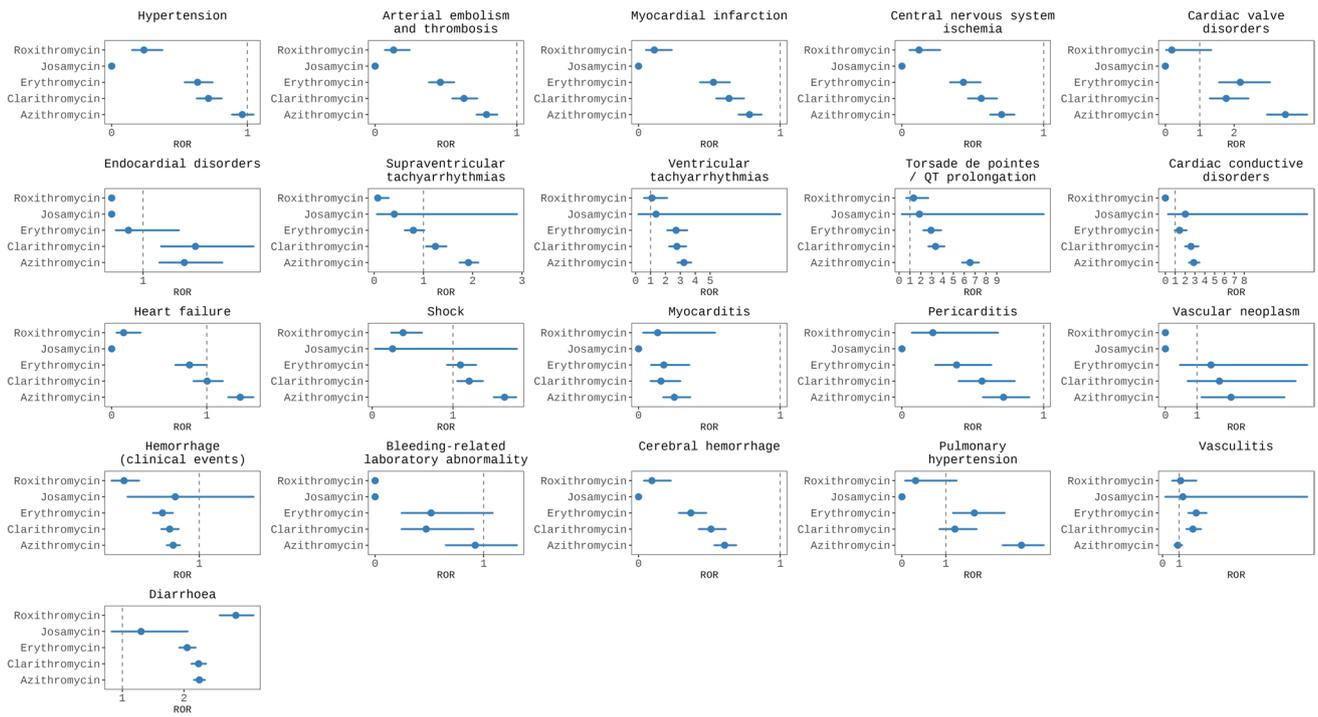
Fig. 2 Disproportionality analysis for reports on female individuals. The forest plot presents the reporting odds ratios (ROR) with 95% confidence intervals for each cardiovascular adverse event
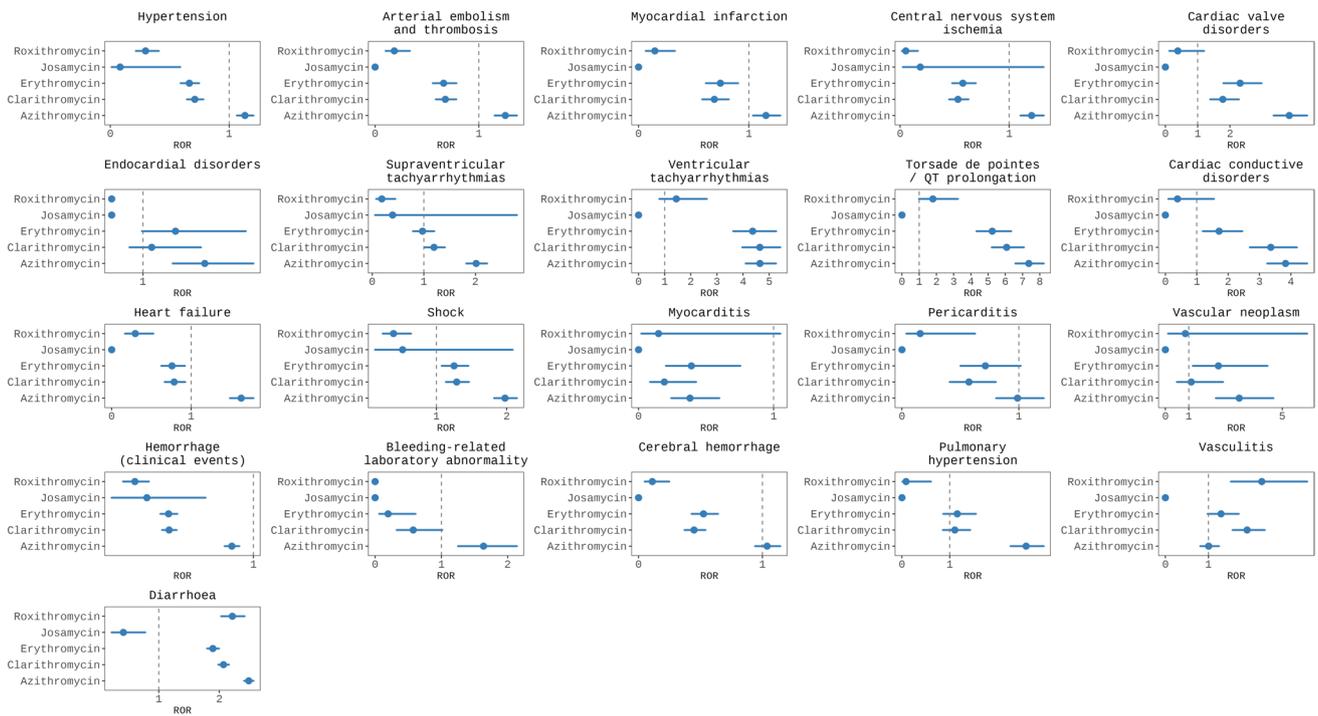
Fig. 3 Disproportionality analysis for reports on male individuals. The forest plot presents the reporting odds ratios (ROR) with 95% confidence intervals for each cardiovascular adverse event
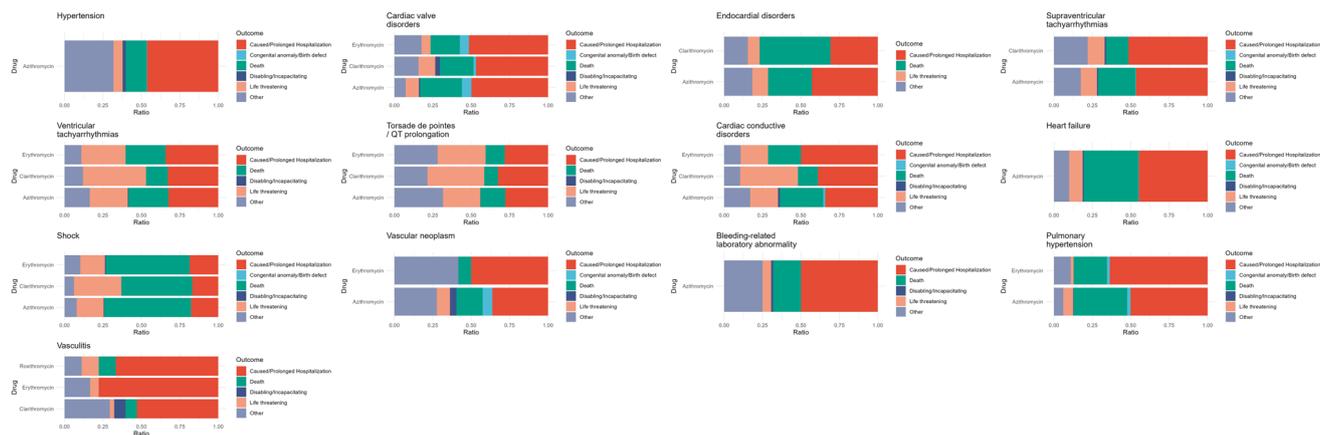
Fig. 4 Patient outcomes. Patient outcomes for drug-cardiovascular toxicity pairs with detected safety signals

and bleeding-related laboratory abnormality were 46%, 45%, and 50%, respectively.

Discussion

In the present study, we investigated the association between macrolides and cardiovascular events using VigiBase, the world's largest safety information database. Macrolide use is considered to be associated with an increased risk of cardiovascular events, including arrhythmias and sudden cardiac death. However, in the present study, we focused on each macrolide drug and various cardiovascular events and performed a comprehensive analysis. Our results suggest that macrolides are associated with an increased risk of arrhythmias, QT prolongation, and TdP, although there are differences in the risks associated with each macrolide. Notably, only azithromycin users reported significantly more adverse events, such as hypertension, heart failure, and bleeding-related laboratory abnormalities. As the five macrolide antimicrobial agents have distinct cardiovascular toxicity profiles, drug-specific monitoring is required for safer drug therapy.

In the present study, we detected a safety signal for QT prolongation for all three macrolide antimicrobial agents. A known mechanism underlying macrolide-induced QT prolongation is that mutations in long QT syndrome (LQTS) types 1–3 (LQT1–3) cause abnormalities in cardiac potassium/sodium channels, resulting in QT prolongation. The half-maximal inhibitory concentration (IC_{50}) values for human ether-a-go-go-related gene (hERG) channels are 39–72, 49, and 1091 (estimated) μM for erythromycin, clarithromycin, and azithromycin, respectively, with the IC_{50} value for azithromycin being approximately 20 times higher than that for erythromycin and clarithromycin [15]. However, the mechanism underlying drug-induced QT prolongation involves not only the direct binding of the drug to the hERG channel and inhibition of the current but also other channel-mediated effects and the inhibition of hERG channel protein translocation to the cell membrane. Therefore, the other contributing factors need to be comprehensively assessed regarding the risk of QT prolongation in real-world clinical practice.

In our study, azithromycin was the only macrolide with a high ROR for heart failure. Coronary artery disease, hypertension, cardiomyopathy, valvular disease, and arrhythmias were considered the causes of heart failure [16–18]. Moreover, the RORs of azithromycin were also higher than those of other drugs for hypertension, cardiomyopathy, and arrhythmia. Therefore, the incidence of heart failure may have been higher owing to these adverse events.

Study Limitations

There were some limitations to the pharmacovigilance and gene expression data used in the present study. First, each drug was administered at different time points. Each drugs have been introduced to the market at varying temporal intervals. Therefore, safety information and health care systems may vary across countries, which could influence the safety reporting outcomes.

In addition, the frequency of reporting certain adverse events tends to increase temporarily after a safety alert is issued, and different reporting dates for various drugs may introduce bias [19]. Second, this study did not consider factors such as patient characteristics, medical history, complications, or concomitant medications, which may result in uneven risk distribution for adverse events between patients using macrolides and those using other non-macrolide drugs. In some cases of QT prolongation, mutations in the potassium voltage-gated channel

subfamily Q member 1 and subfamily H member 2 as well as sodium channel protein type 5 subunit alpha, which are the genes associated with LQT1–3, were identified. This suggests that a latent form of congenital LQTS (Forme Fruste) could be a possible cause. Patients experiencing QT prolongation may have latent QT prolongation, and there may be a similar imbalance in patient distribution for other cardiovascular diseases. Third, the present study does not consider the impact of different dosages or treatment durations on the observed cardiovascular toxicity profiles, which could be important factors in determining risk. These factors are crucial for evaluating the intensity of drug exposure, and there may be differences in exposure levels between different drugs.

Conclusion

In conclusion, this study contributes to a deeper understanding of the differences in the cardiovascular toxicity profiles of macrolide antimicrobial agents. The results revealed that each macrolide exhibits a different cardiovascular toxicity profile, despite with various limitations. Our findings may help inform the development of appropriate monitoring strategies in real-world clinical practice. In the future, it is expected that drug selection will be guided by the cardiovascular toxicity profile of each macrolide.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval This study was approved by the Ethics Committee of Tokushima University Hospital (approval number: 4492).

Research Involving Human and Animal Participants All procedures involving human participants adhered to ethical standards set by the institutional research committee and followed the principles of the Declaration of Helsinki.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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