Medicines Adverse Reactions Committee

Meeting date	12/06/2025	Agenda item	3.2.4
Title	**Macrolides and cardiovascular death**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Azithromycin	Azithromycin AFT injection	AFT Pharmaceuticals Ltd
	Zithromax tablets and oral suspension	Pfizer New Zealand Ltd
Erythromycin	E-Mycin tablet and oral suspension	Viatris Limited
	ERA tablets	AFT Pharmaceuticals Ltd
	Erythrocin IV injection	AFT Pharmaceuticals Ltd
Clarithromycin	Klacid tablets, oral suspension and IV injection	Viatris Limited
Roxithromycin	Arrow-Roxithromycin tablets	Teva Pharma (New Zealand) Ltd

PHARMAC funding	Funded
Previous MARC meetings	Macrolides and risk of cardiac arrythmias (161st meeting on 12 March 2015).
Prescriber Update	Macrolides – Don't Upset the Rhythm (June 2015) Drug-induced QT prolongation and Torsade de Pointes – the facts (December 2010)
Classification	Prescription medicine

Advice sought	**The Committee is asked to advise:**
	• On the strength of the evidence in the scientific literature for an association between
	  ○ azithromycin
	  ○ erythromycin
	  ○ clarithromycin
	  ○ roxithromycin
	and an increased risk of cardiovascular death.
	• Whether a warning statement (section 4.4) is required in all macrolide data sheets, or only certain macrolides?
	• Whether the term cardiovascular death should be included as an undesirable effect (section 4.8) in all macrolide data sheets or only certain macrolides?
	• Whether further communication is required, other than in MARC's remarks?

Table of Contents

1 PURPOSE

In 2021, the US Food and Drug Administration (FDA) requested updates to the azithromycin product information, to include the risk of cardiovascular death in the 'warnings and precautions' section and as an adverse reaction. The request followed the results of epidemiological studies which had observed a two-fold increased risk of cardiovascular death in adults exposed to azithromycin relative to other antibiotics, such as amoxicillin. This risk appeared to be the greatest during the first five days of azithromycin use [1].

Similar updates have also been implemented to the Australian azithromycin product information.

The New Zealand azithromycin innovator data sheet, Zithromax, currently does not include information on cardiovascular death but lists the following undesirable effects relating to the cardiovascular system: hypotension; palpitations and arrhythmias including ventricular tachycardia. The data sheet also states that there have been rare reports of QT prolongation and torsades de pointes (TdP).

Although recent international action has focused on azithromycin and the risk of cardiovascular death, this paper will also consider other macrolide antibiotics (ie, erythromycin, clarithromycin and roxithromycin) and the risk of cardiovascular death.

The Medicines Adverse Reactions Committee is asked to consider the strength of the evidence of an increased risk of cardiovascular death from macrolide antibiotics and whether regulatory action is warranted.

2 BACKGROUND

2.1 Macrolide antibiotics

Macrolides are a class of antibiotics used to treat various bacterial infections. They have an antibacterial spectrum that is similar but not identical to penicillin, and are therefore an alternative in penicillin-allergic patients [2].

Macrolides are bacteriostatic as they inhibit bacterial protein synthesis by binding to the bacterial 50S ribosome. They are also thought to have anti-inflammatory and immunomodulatory effects [3]. These properties are useful in the treatment of chronic lung diseases (such as bronchiectasis, bronchiolitis obliterans, and cystic fibrosis) [2].

In New Zealand, the approved macrolides are azithromycin, erythromycin, clarithromycin and roxithromycin.

2.2 Macrolides and effect on the QT interval

Macrolides have the propensity to prolong the QT interval in the cardiac cycle [3]. The underlying mechanism is thought to be inhibition of the flow of potassium by blocking the current that repolarises the cardiomyocytes (this current is known as I_{Kr}) [4].

Available mechanistic data comparing individual macrolides suggest that clarithromycin and erythromycin have higher potency of I_{kr} inhibition compared with roxithromycin, and thus higher potential for QT prolongation and proarrhythmic properties. Azithromycin shows the weakest blockade of I_{kr} *in vitro*, although a study suggests this might not be the case *in vivo* [4].

Cardiac events and fatal arrythmias may occur when the QT interval is prolonged. Excessive QT prolongation can predispose patients to develop TdP. TdP is a form of polymorphic tachycardia. Episodes of TdP can recur in rapid succession, potentially degenerating to ventricular fibrillation and sudden cardiac death [5].

Comments:

In 2015 Medsafe sought advice from the MARC based on a safety signal originating from the literature in which macrolide antibiotic treatment was found to be associated with an increased risk of cardiac arrhythmia and sudden death. The Committee noted that information on QT interval prolongation in the

various data sheets for macrolides is not consistent. The Committee recommended that Medsafe request the sponsors of azithromycin, clarithromycin, erythromycin and roxithromycin to update the precautions, interactions and contraindications sections of the data sheets so that the information is consistent across all macrolide data sheets.

2.3 Sudden cardiac death and cardiovascular mortality definitions

2.3.1 Sudden cardiac death

Sudden cardiac death (SCD) is defined as death presumed to be of a cardiac cause that occurs within an hour of onset of cardiac symptoms or 24 hours of last being seen healthy and alive. Autopsies may reveal a cardiac aetiology, though not all SCD cases have an identifiable cause. SCD mostly results from an electrical accident in the form of ventricular arrhythmias or asystole. Some patients have an anatomic and functional substrate for developing life-threatening ventricular arrhythmias or asystole. However, many have transient events in the form of myocardial ischemia or infarction, metabolic abnormalities, and drug toxicities leading to ventricular tachyarrhythmias or asystole [6].

2.3.2 Cardiovascular mortality

Cardiovascular mortality is defined as death due to diseases of the heart or blood vessels, most commonly coronary heart disease, sudden cardiac death, or stroke [7]. In New Zealand, cardiovascular disease is the leading cause of death, and includes heart, stroke, and blood vessel disease. Almost 1 in 3 deaths are caused by cardiovascular disease [8].

2.4 Data sheets

2.4.1 New Zealand

Table 1 shows the New Zealand macrolide data sheet wording on QT prolongation and cardiovascular death, if any. The current funded brand was reviewed if the innovator product was not available.

Table 1: Review of macrolide data sheets and information on cardiovascular death and QT prolongation (warning on cardiovascular death is highlighted in yellow)

Azithromycin	
Zithromax	**Section 4.4** *Prolongation of the QT interval* Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products including azithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of azithromycin for at-risk groups including: • patients predisposed to QT interval prolongation • patients taking other medications known to prolong the QT interval such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones • patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia • patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency • elderly patients, as they may be more susceptible to drug-associated effects on the QT interval. **Section 4.8** *Cardiovascular disorders:* hypotension; palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes.
Erythromycin	
E-Mycin (erythromycin ethyl succinate)	**Section 4.3** • Congenital or acquired QT interval prolongation • Concomitant intake of medicinal products, which can lead to prolongation of the QT interval and under some circumstances to life-threatening ventricular arrhythmia (torsade de pointes) e.g. terfenadine,

	astemizole, domperidone, cisapride, pimozide, class IA and III antiarrhythmics (e.g. disopyramide), certain neuroleptics, tri- and tetracyclic antidepressants, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole anti-mycotics and anti-malarials (e.g. pentamidine i.v.) (see section 4.5) **Section 4.4** *QTc prolongation* Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the administration of erythromycin. Therefore, use of erythromycin is contraindicated in patients with high risk factors for cardiac arrhythmia (see Section 4.3 CONTRAINDICATIONS) and should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia. If during therapy with erythromycin symptoms such as palpitations, dizziness or syncope occur which can be signs of arrhythmia, an investigation of the patient including electrocardiogram and determination of the QT interval should be initiated immediately. Electrolyte disturbances promote the probability of cardiac arrhythmia. In the case of risk factors for electrolyte disturbances (such as diuretic/laxative medication, vomiting, diarrhoea, use of insulin in emergency situations, renal diseases or anorectic conditions), adequate laboratory tests and if necessary an adequate electrolyte balance should be carried out. **Section 4.5** *Medicines that prolong the QTc interval* Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsade de pointes in some patients. Patients with uncorrected electrolyte disorders particularly hypokalaemia; known prolongation of the QTc interval, or those concurrently receiving medicines that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmics, certain neuroleptics, tri- and tetracyclic antidepressants, ebastine, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole anti-mycotics and anti-malarial medicines (e.g. pentamidine i.v.), are at increased risk of ventricular arrhythmias. As these predisposing conditions may increase the risk for ventricular arrhythmias, erythromycin should not be used in patients with ongoing proarrhythmic conditions (see Section 4.3). *Medicines metabolised by the cytochrome P450 system* Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsades de pointes in some patients. In one published study patients who used both oral erythromycin and strong CYP3A inhibitors (azole antifungal medicines [ketoconazole, itraconazole and fluconazole, all administered systemically], diltiazem, verapamil, troleandomycin, mibefradil, nefazodone) had a risk of sudden death from cardiac causes that was five times as great as that among patients who had not used these medicines. Many of the medicines that are known to block CYP3A4 also have direct effects on repolarisation, which may cause a dramatic lengthening of the QT interval. Given that there are alternatives to erythromycin and these listed CYP3A inhibitors, the use of these combinations should be avoided. **Section 4.8** *Cardiac disorders* Rare: QT interval prolongation, cardiac arrhythmias such as ventricular tachycardia (torsade de pointes), cardiac arrest and palpitation
ERA tablets (erythromycin stearate)	**Section 4.3** • Erythromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5) • Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval). **Section 4.4** *Cardiovascular Events* Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8). Fatalities have been reported. *Erythromycin should be used with caution in the following* • Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.

	• Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5) • Elderly patients may be more susceptible to drug- associated effects on the QT interval (see section 4.8). • Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin. **Section 4.5** *QT prolongation medicines* • There is a rare risk of serious cardiovascular adverse events, including QT interval prolongation, cardiac arrest, torsades de pointes and cardiac arrhythmias, with erythromycin alone and with the concomitant administration of erythromycin with other medicines that prolong the QT interval. • Examples of medicines that prolong the QT interval include class IA and III antiarrhythmics (e.g. amiodarone), antipsychotics (e.g risperidone, haloperidol), antidepressants (e.g. citalopram) and fluoroquinolones (e.g. ciprofloxacin) (see section 4.4). **Section 4.8** *Cardiac disorders:* Cardiac arrest, ventricular fibrillation (frequency not known).
Clarithromycin	
Klacid	**Section 4.3** • Concomitant administration of clarithromycin and any of the following medicines is contraindicated: astemizole, cisapride, domperidone, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.4 and 4.5). • Clarithromycin must not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5). • Clarithromycin must not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia due to the risk of prolongation of the QT interval). **Section 4.4** *Cardiovascular events* Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin is contraindicated in the following situations: • Clarithromycin must not be given to patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia (see section 4.3). • Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide and terfenadine is contraindicated (see section 4.3). • Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3). Clarithromycin should be used with caution in the following patients: • Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia. • Patients concomitantly taking other medicinal products associated with QT prolongation, other than those which are contraindicated (see section 4.5). Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin. **Section 4.5** [Note: this section outlines various medicines that can interact with clarithromycin by prolonging the QT interval. Refer to the data sheet]. **Section 4.8**

	Uncommon: Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations Not known: Torsade de pointes, ventricular tachycardia ventricular fibrillation
Roxithromycin	
Arrow-Roxithromycin	**Section 4.4** *Prolongation of the QT Interval* Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide antibiotics including roxithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of roxithromycin for at-risk groups including: • Patients predisposed to QT interval prolongation such as those with a history of torsades de pointes or congenital long QT syndrome. • Patients taking other medication known to prolong the QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones. • Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia. • Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency. **Section 4.5** [Note: this section outlines various medicines that can interact with roxithromycin by prolonging the QT interval. Refer to the data sheet]. **Section 4.8** QT prolongation

Comments:

There is consistent warning on the risk of QT prolongation and TdP across the macrolide data sheets. Some data sheets also mention that fatalities have been reported from QT prolongation.

With regards to cardiovascular deaths (not specifically relating to QT prolongation and sudden cardiac death), the ERA (erythromycin stearate) and Klacid (clarithromycin) data sheets has the following warning in section 4.4:

> *Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including [macrolide name]. Consideration of these findings should be balanced with treatment benefits when prescribing [macrolide name].*

Interestingly, the other erythromycin salt (ethyl succinate) does not have this warning.

2.4.2 International product information

Table 2 shows the various macrolide antibiotics prescribing information from Australia, the UK, US and Canada, and whether there is information on cardiovascular death/mortality.

Table 2: International product information for macrolides – cardiovascular death/mortality information

Macrolide	Australia	UK	US	Canada
Azithromycin	Zithromax *Section 4.4* Cardiovascular death Some observational studies have shown an approximately two-fold increased short-term potential rare risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The data in these observational studies are insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use. This potential risk was noted to be greater during the first five days of azithromycin use. In patients whose medical history and/or on-going medical treatments place them at high risk for a prolonged QTc, consider performing a screening ECG. Consider balancing this potential risk with treatment benefits when prescribing Zithromax. *Section 4.8* Cardiovascular disorders: cardiovascular death	Azithromycin 500mg tablets *Section 4.4* Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.	Zithromax *Warnings and precautions* Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The five-day cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithromycin use and does not appear to be limited to those patients with preexisting cardiovascular diseases. The data in these observational studies are insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use. Consider balancing this potential risk with treatment benefits when prescribing ZITHROMAX. *Post-marketing experience* There have been reports of... cardiovascular death.	Zithromax No information.
Erythromycin	E-mycin: No info. Erythrocin IV: *Section 4.4* Cardiovascular events Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia,	Erythromycin Tablets BP *Section 4.4* Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of	ERY-PED No information.	Erythrocin *Serious warnings and precautions* Cardiovascular events Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including

	myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.	these findings should be balanced with treatment benefits when prescribing erythromycin.		erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.
Clarithromycin	**Klacid** *Section 4.4* Cardiovascular events Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin	**Clarithromycin 500 mg tablets** *Section 4.4* Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.	**Biaxin** No information.	**Sandoz Clarithromycin** *Warnings and precautions* Cardiovascular events Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Studies have identified risks of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.
Roxithromycin	**Roxithromycin Sandoz** No information.	No product	No product.	No product.

Comments:

There is consistent warning in the data sheets for clarithromycin and erythromycin regarding an increased risk of cardiovascular death in epidemiological studies:

> *Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including [macrolide name]. Consideration of these findings should be balanced with treatment benefits when prescribing [macrolide name].*

For azithromycin, the US and Australian product information has specific warning on the short term (5 days) risk of cardiovascular death. This may reflect more specific literature for this macrolide warranting a more specific warning. However, some differences in the Australian and US product information are noted:

- The US labelling says that the risk does not appear to be limited to those with pre-existing cardiovascular disease.
- The Australian product information advising to consider performing a screening ECG in patients whose medical history and/or on-going medical treatments place them at high risk for a prolonged QTc.

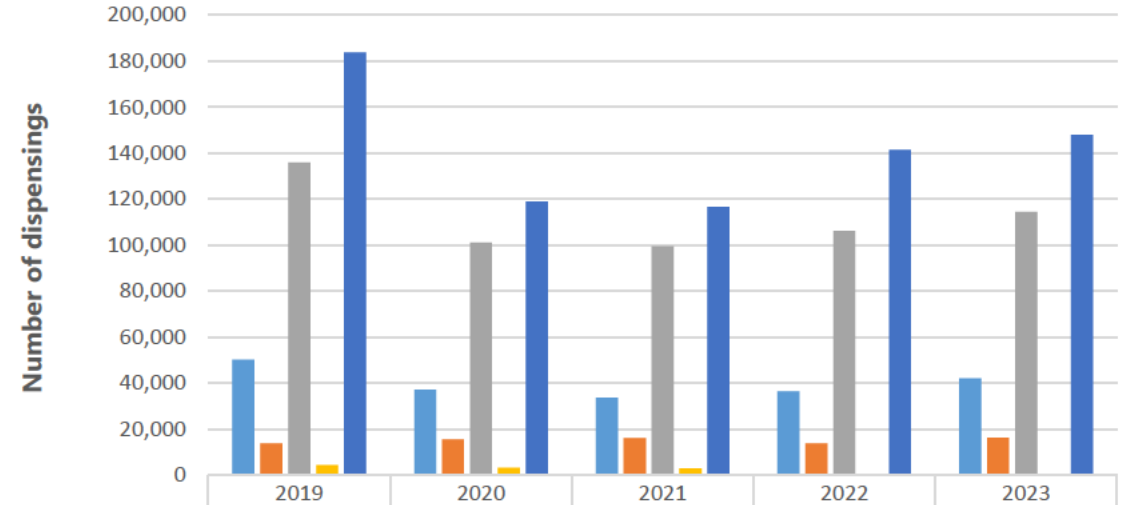
Roxithromycin is not approved/registered in the above jurisdiction except in Australia. There is no warning on cardiovascular death.

2.5 Usage

Figure 1 shows macrolide usage data by the number of (a) dispensings and (b) the number of people who received a dispensing from 2019 to 2023.

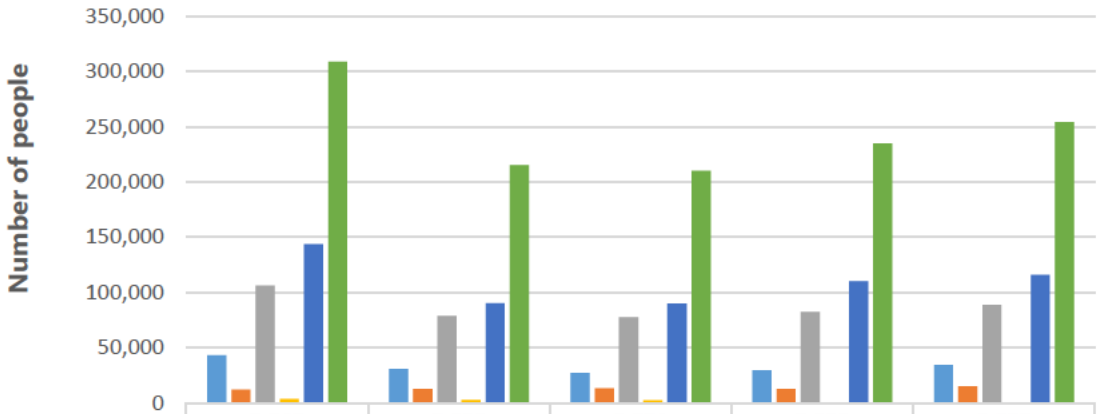
Figure 1: Usage of macrolides in New Zealand from 2019 to 2023

(a) Number of initial dispensing[a]



	2019	2020	2021	2022	2023
Azithromycin	50,122	37,184	33,779	36,463	42,062
Clarithromycin	13,920	15,467	16,067	13,869	16,260
Erythromycin ethyl succinate	135,981	101,134	99,401	106,141	114,543
Erythromcyin stearate	4,418	3,337	2,993	532	
Roxithromycin	183,844	118,894	116,554	141,316	147,869

(b) Number of people[b]



	2,019	2,020	2,021	2,022	2,023
Azithromycin	43,317	30,785	27,227	29,504	34,530
Clarithromycin	11,831	12,722	13,249	12,468	14,937
Erythromycin ethyl succinate	106,075	78,705	77,416	82,365	88,748
Erythromcyin stearate	3,485	2,670	2,393	475	
Roxithromycin	143,893	90,255	89,800	110,090	115,900
Class	308,601	215,137	210,085	234,902	254,115

Notes:

a. Dispensings: Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.
b. People: Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Te Whatu Ora Health New Zealand Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 21 May 2025).

3 SCIENTIFIC INFORMATION

3.1 Published literature

This literature review consists of three sections: (1) for azithromycin, (2) other individual macrolides and (3) macrolides as a class.

Literature review for azithromycin

3.1.1 Zaroff et al (2020) – Association of azithromycin use with cardiovascular mortality [9]

Aim: This retrospective cohort study examined the risk of cardiovascular death and sudden cardiovascular death associated with outpatient use of oral azithromycin compared to amoxicillin, an antibiotic not known to increase cardiovascular events.

Methods: The cohort consisted of members receiving healthcare from Kaiser Permanente California, a diverse racial and socioeconomic population. People were included if they received an outpatient prescription for oral azithromycin or amoxicillin (or amoxicillin + clavulanic acid) between 1998 to 2014, and aged 30-74 years of age. People were excluded if they received both antibiotics, had serious underlying medical conditions, or were hospitalised during the 30 days before the index date (date of prescription), or residing for more than 30 days in a nursing home in the 365 days prior to the index date.

The primary outcomes were cardiovascular death and sudden cardiac death. Cardiovascular death was defined as death with an underlying cardiovascular cause (eg, myocardial infarction, heart failure, arrythmia, stroke). Secondary outcomes were all-cause death and non-cardiovascular death.

The analysis was restricted to exposure windows of 0 to 5 and 6 to 10 days after the index date (date the prescription was dispensed) as a hypothesised mechanism of harm is potential increased risk of cardiac arrhythmia during therapy and the typical duration of use for azithromycin and amoxicillin is between 7 to 10 days.

Results (only cardiovascular death and sudden cardiac death is presented below): The cohort included 7,824,681 antibiotic exposures, including 1,736,976 azithromycin exposures (22.2%) and 6,087,705 amoxicillin exposures, among 2,929,008 unique individuals. The mean age was 50.7 years (SD 12.3 years).

Compared with amoxicillin, patients receiving azithromycin were at significantly higher risk of cardiovascular death (HR= 1.82; 95% CI 1.23-2.67) but not sudden cardiac death (HR=1.59; 95% CI 0.90-2.81) within 5 days of the index date. The results were not significant within 6 to 10 days after the index date (Table 3).

Table 3: Cardiovascular death and sudden cardiac death after azithromycin and amoxicillin exposure

[redacted]

A total of 485 deaths occurred within 10 days of a study antibiotic index date. Of these deaths, 256 (52.8%) were cardiovascular deaths. Among cardiovascular deaths, 112 (44%) were classified as sudden cardiac deaths.

The adjusted risk difference for cardiovascular death for azithromycin within 5 days of the index date was 12.79 (95% CI, 3.66-26.21) per 1,000,000 prescriptions. There was an increased risk of cardiovascular death within 5 days for those in the top decile of the cardiovascular risk score (HR= 1.71; 95% CI 1.06-2.76) (Table 4).

Table 4: Cardiovascular Death and Sudden Cardiac Death After Azithromycin and Amoxicillin Exposure

[redacted]

Author's conclusions: This cohort study found an approximately 2-fold increased risk of cardiovascular death after outpatient azithromycin use compared with use of amoxicillin within a 5-day window after dispensing but not within 6 to 10 days after dispensing. Though a proportion of the cardiovascular deaths observed were sudden deaths and thus suggestive of arrhythmia, there were more deaths related to other cardiac conditions. There is not a clear mechanism to explain how azithromycin would directly cause those deaths.

3.1.2 Ray et al (2012) – Azithromycin and risk of cardiovascular death [10]

Aim: This retrospective cohort study compared the risk of cardiovascular death in people taking azithromycin compared to those who did not take antibiotics and who took other selected antibiotics. The authors

hypothesised that patients taking azithromycin have a higher risk of cardiovascular death, particularly sudden cardiac death because of the proarrhythmic effects of azithromycin.

Methods:

The cohort were patients enrolled in the Tennessee Medicaid programme who were prescribed azithromycin between 1992 to 2006, aged 30-74 years, had no life-threatening non-cardiovascular illness and met the eligibility criteria. The criteria were designed to exclude patients at high risk of death from causes unrelated to a short-term effect of proarrhythmic medicines.

The study also included propensity score matched control periods (of similar length to the courses of antibiotic therapy) during which there was no use of study antibiotics. For each qualifying azithromycin prescription, four such control periods were identified, which were frequency-matched.

Lastly additional control groups were created to minimise confounding by indication:

- amoxicillin (with or without clavulanic acid) – has indications similar to those being given azithromycin but no known proarrhythmic effect.
- ciprofloxacin, and levofloxacin – also similar indications to azithromycin. Ciprofloxacin is thought to have limited proarrhythmic effect and levofloxacin a greater potential to have proarrhythmic potential than ciprofloxacin.

Two different exposure periods were used: a 5-day period that is generally recommended for azithromycin and the 10-day period most commonly suggested for the other study antibiotics.

The primary endpoints were cardiovascular death and death from any cause.

To provide a summary measure of the risk of cardiovascular death, a risk score for cardiovascular disease was calculated. This score estimated the probability of cardiovascular death (in the absence of use of a study antibiotic) as a function of the indicators of coexisting conditions.

Results:

The study cohort included persons with 347,795 prescriptions for azithromycin, 1,391,180 matched control periods with no study antibiotic treatment, 1,348,672 prescriptions for amoxicillin, 264,626 prescriptions for ciprofloxacin, and 193,906 prescriptions for levofloxacin. Mean age was approximately 50 years.

When a 5-day course of azithromycin therapy was compared with a matched period of no antibiotic treatment, azithromycin was associated with an increased risk of both cardiovascular death, sudden cardiac death, non-cardiovascular ('other cause') death and death from any cause (Table 5).

Table 5: Cumulative Incidence of Death among Patients during a 5-Day Course of Azithromycin, as Compared with Persons Who Received No Antibiotic Treatment and Patients Who Took Amoxicillin, According to Cause of Death.

A 5-day course of azithromycin therapy, as compared with the first 5 days of a course of amoxicillin therapy, was associated with significant increases in the risk of both cardiovascular death (hazard ratio, 2.49; 95% CI, 1.38 to 4.50; P=0.002) and death from any cause (hazard ratio, 2.02; 95% CI, 1.24 to 3.30; P=0.005). Thus, patients who took azithromycin had an estimated 47 additional cardiovascular deaths per 1 million 5-day courses of therapy.

A 5-day course of azithromycin compared to ciprofloxacin was associated with an increased risk of cardiovascular death (hazard ratio, 3.49; 95% CI, 1.32 to 9.26; P=0.01) and a nonsignificant trend toward an increase in death from any cause (hazard ratio, 1.75; 95% CI, 0.91 to 3.37; P=0.09). In contrast the risk did not differ with levofloxacin.

The absolute excess risk of cardiovascular death for patients who took azithromycin, as compared with those who took amoxicillin, varied according to the baseline risk score for cardiovascular disease. For patients in the highest decile of risk scores, who accounted for 59% of the cardiovascular deaths during azithromycin therapy, there were an estimated 245 additional cardiovascular deaths per 1 million 5-day courses of azithromycin therapy (Figure 2).

Figure 2: Excess Risk of Cardiovascular Death with Azithromycin as Compared with Amoxicillin, According to Decile of Cardiovascular Risk Score

Discussion and conclusions:

A 5-day course of azithromycin was associated with a small absolute increase in the risk of cardiovascular death, which was most pronounced for patients in the highest decile of the baseline risk of cardiovascular disease. There was no increased risk of death from non-cardiovascular causes among patients who took azithromycin, but there was an increase in the risk of death from any cause. The risk of cardiovascular death was significantly greater with azithromycin than with either amoxicillin or ciprofloxacin (antibiotics not known to have a proarrhythmic effect) but did not differ significantly from the risk with levofloxacin (an antibiotic though to have proarrhythmic potential).

3.1.3 Assimon et al (2022) – Azithromycin use increases the risk of sudden cardiac death in patients with haemodialysis-dependent kidney failure [11]

Aim: Retrospective cohort study comparing the 5-day risk of sudden cardiac death (SCD) in haemodialysis patients receiving azithromycin with patients receiving amoxicillin or levofloxacin. Haemodialysis patients were specifically examined as this population has a high prevalence of cardiovascular disorders but were excluded from azithromycin clinical studies.

Methods:

Using the United States Renal Data System database, all outpatient prescriptions for azithromycin, amoxicillin based antibiotics (amoxicillin with or without clavulanic acid) and levofloxacin filled between 2007 to 2017 were screened and two cohorts were created to compare (1) azithromycin vs. amoxicillin-based antibiotics (amoxicillin and amoxicillin/clavulanic acid) and (2) azithromycin vs. levofloxacin. In both cohorts, study antibiotic treatment episodes consisted of a 180-day baseline period, a 30-day washout period, and a 10-day follow-up period.

The primary outcome of interest was SCD, defined as death from cardiac arrhythmia or cardiac arrest listed as the primary cause.

The risk of SCD during days 1–5 and 6–10 was assessed separately. During each study antibiotic treatment episode, individuals were followed forward in time during the two outcome periods for the first occurrence of SCD.

Post-hoc analysis: An additional new-user cohort comprised of azithromycin, levofloxacin, and amoxicillin-based antibiotic treatment episodes was constructed to examine gradation of risk across all three classes of antibiotics. Using analogous methods to both two-drug cohorts, the authors examined the comparative

cardiac safety of azithromycin and levofloxacin vs. amoxicillin-based antibiotics in the three-drug cohort during days 1–5, a time period that captures active use of all study medications based on typical prescription durations.

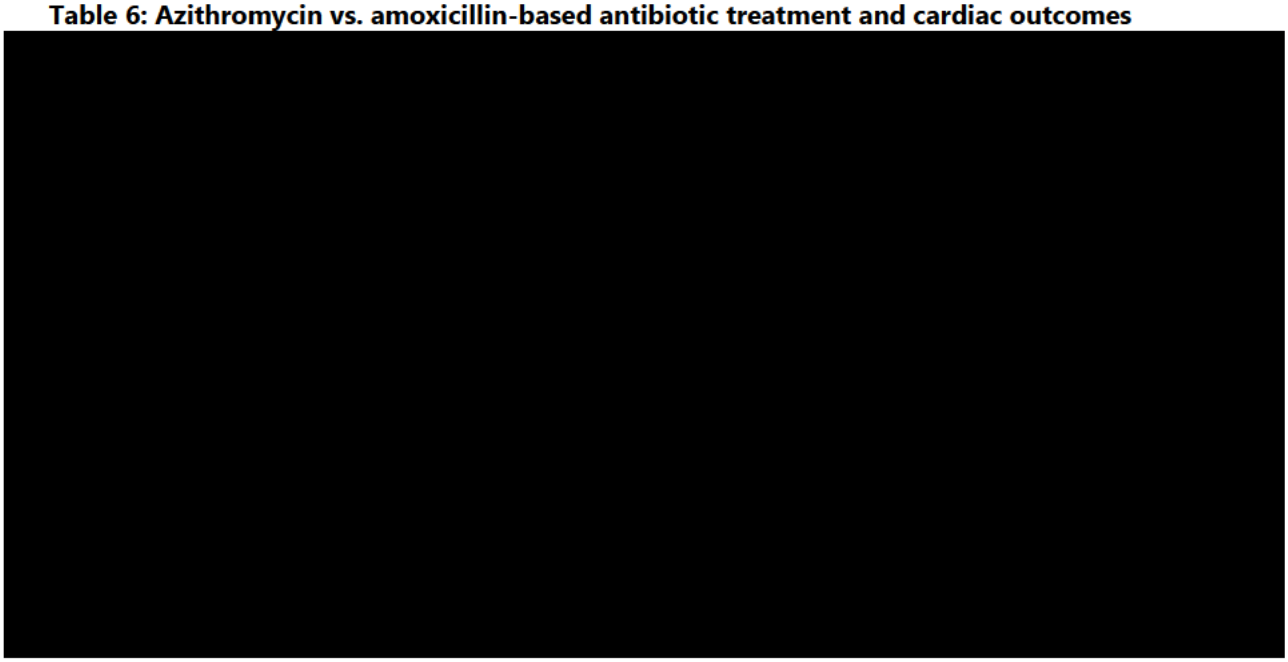
Results:

Azithromycin vs amoxicillin

A total of 725,431 antibiotic treatment episodes among 282,899 unique adults receiving in-centre haemodialysis were included: 381,306 (52.6%) azithromycin treatment episodes (187,383 patients) and 344,125 (47.4%) amoxicillin-based antibiotic treatment episodes (174,551 patients).

Compared with amoxicillin-based antibiotic, azithromycin was associated with a higher risk of SCD during days 1–5 (Table 6), with a weighted HR of 1.70 (95% CI, 1.36 to 2.11) and weighted RD per 100,000 treatment episodes of 25.0 (95% CI, 15.5 to 36.5). The association was not significant during days 6–10, with a weighted HR of 1.22 (95% CI, 0.98 to 1.51).

Table 6: Azithromycin vs. amoxicillin-based antibiotic treatment and cardiac outcomes



Azithromycin vs levofloxacin

A total of 554,557 antibiotic treatment episodes among 245,143 unique adults receiving in-centre haemodialysis were included: 387,382 (69.9%) azithromycin treatment episodes (188,871 patients) and 167,175 (30.1%) levofloxacin treatment episodes (110,230 patients).

Compared with levofloxacin, azithromycin was associated with a lower risk of SCD during days 1–5, with a weighted HR of 0.79 (95% CI, 0.64 to 0.96) (Table 7). The association was similar during days 6–10, with a weighted HR of 0.78 (95% CI, 0.62 to 0.97).

Table 7: Azithromycin vs. levofloxacin treatment and cardiac outcomes

[redacted]

Post-hoc analyses: azithromycin and levofloxacin vs. amoxicillin-based antibiotics

A total of 865,542 antibiotic treatment episodes among 316,588 unique adults receiving in-centre haemodialysis were included in the three-drug cohort: 158,659 (18.3%) levofloxacin treatment episodes (106,083 patients), 371,132 (42.9%) azithromycin treatment episodes (184,461 patients), and 335,751 (38.8%) amoxicillin-based antibiotic treatment episodes (171,798 patients).

Compared to amoxicillin-based antibiotic treatment, levofloxacin treatment was associated with the highest risk of SCD during days 1–5 (Figure 3). SCD risk was elevated during azithromycin treatment but was lower than the risk associated with levofloxacin treatment.

Figure 3: Levofloxacin and azithromycin vs. amoxicillin-based antibiotics and sudden cardiac death during days 1–5

[redacted]

Discussion and conclusions:

In patients on haemodialysis, treatment with azithromycin had a higher risk of SCD compared with those treated with amoxicillin-based antibiotics and a lower risk of SCD compared to those treated with levofloxacin.

Patients on haemodialysis have pre-existing cardiac vulnerability that put them at risk of cardiac arrythmias. These include electrolyte abnormalities, polypharmacy and a high prevalence of cardiovascular disorders. These factors together with talking medicines that prolong ventricular repolarisation such as azithromycin and levofloxacin can increase the risk of SCD.

3.1.4 Rao et al (2014) – Azithromycin and Levofloxacin Use and Increased Risk of Cardiac Arrhythmia and Death [12]

Aim: This retrospective cohort study evaluated a national cohort of US veterans receiving care at the Department of Veterans Affairs (VA) between September 1999 and April 2012 to investigate whether increased cardiac arrhythmia and mortality risks were observed in a population of older male individuals receiving either azithromycin, amoxicillin, or levofloxacin.

Methods:

Eligible patients were 30-74 years of age with no life-threatening non-cardiovascular illness, no diagnosis of drug abuse, not residing in a nursing home, no hospitalisation in the last 30 days. Only outpatient antibiotic dispensings were included.

Primary and secondary endpoints were all-cause mortality and serious cardiac arrythmias, defined as any inpatient or emergency department encounter for long QT syndrome, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or cardiac arrest.

Follow-up times were separated into the first 5 days and days 6 through 10 after antibiotics were dispensed, with day 1 being the first day the drug was dispensed. The authors compared patients who during the evaluation period received exclusively azithromycin, levofloxacin, or amoxicillin within 30 days after a VA outpatient visit.

Results:

More than 1.6 million unique antibiotics were dispensed: 979,380 amoxicillin, and 594,792 azithromycin, and 201,798 levofloxacin. The entire cohort of patients had a mean age of 56.5 years.

At days 1 to 5, compared with amoxicillin, treatment with azithromycin had a 1.48-fold increased risk of death (95% CI, 1.05–2.09) and a 1.77-fold increased risk of development of serious arrhythmias (95% CI, 1.56–3.79). At days 6 to 10, risks of death and serious arrhythmia were similar for azithromycin and amoxicillin (hazard ratio [HR] = 1.14, 95% CI, 0.81–1.62, and HR = 1.37, 95% CI, 0.91–2.05, respectively) but remained statistically significant for levofloxacin (HR = 1.75, 95% CI, 1.09–2.82).

Discussion and conclusion:

Compared with amoxicillin, a short course of azithromycin therapy was associated with a significantly increased risk of mortality and serious arrythmias within the first 5-days of treatment. The risk of these events was not significant from days 6 to 10. Levofloxacin, which was predominantly dispensed for a minimum of 10 days, resulted in an increased risk throughout the 10-day period.

The strengths of this study include a very large sample size and adjustment for covariates that were not available in previous studies (such as baseline laboratory values, smoking history and BMI). A limitation is that patients with high-risk comorbidities or/and higher disease severity may be more likely to be given prescriptions for such broad-spectrum antibiotics as levofloxacin and azithromycin, which might bias the mortality results away from the null. Even so, considering the number and diversity of the covariates, balanced with IPTW, including antibiotics indication, comorbidities, variety of laboratory test results, and medications, the effect of possible residual imbalance is minimised.

Comments:
This study looked at all-cause mortality not specifically cardiovascular mortality.

3.1.5 Svanstrom et al (2013) – Use of azithromycin and death from cardiovascular causes [13]

Aim: This prospective cohort study investigated whether azithromycin was associated with an increased risk of death from cardiovascular causes, compared with no antibiotic use and with the use of penicillin V.

Methods:

The cohort was sourced from the Danish Civil Registration System and included people in Denmark aged 18 to 64 years of age between 1997 to 2010. The study was limited to a population of young and middle-aged adults because both the baseline risk of death from cardiovascular causes and the indications for azithromycin are heterogeneous across the age group.

Participants used either oral azithromycin or penicillin V, and could have multiple prescriptions during the study period. Participants were included if they had not been hospitalised and not used any antibiotics within 30 days before the index date.

The timing of treatment was classified as current use (1 to 5 days, starting from the index date), recent use (6 to 10 days), and past use (11 to 35 days).

The primary outcome was cardiovascular death, and the secondary outcome was death from other causes.

A subgroup analysis was carried out looking at the risk of cardiovascular death in subgroups according to sex, age, and status with respect to a history of cardiovascular disease.

Result:

The study inclusion criteria were met for 1,102,419 episodes of azithromycin use, 7,364,292 episodes of penicillin V use, and 7,084,185 control episodes of no antibiotic use. After propensity-score estimation and matching in a 1:1 ratio, the cohort used in the analysis of azithromycin versus no use of antibiotics included a total of 2,204,100 episodes.

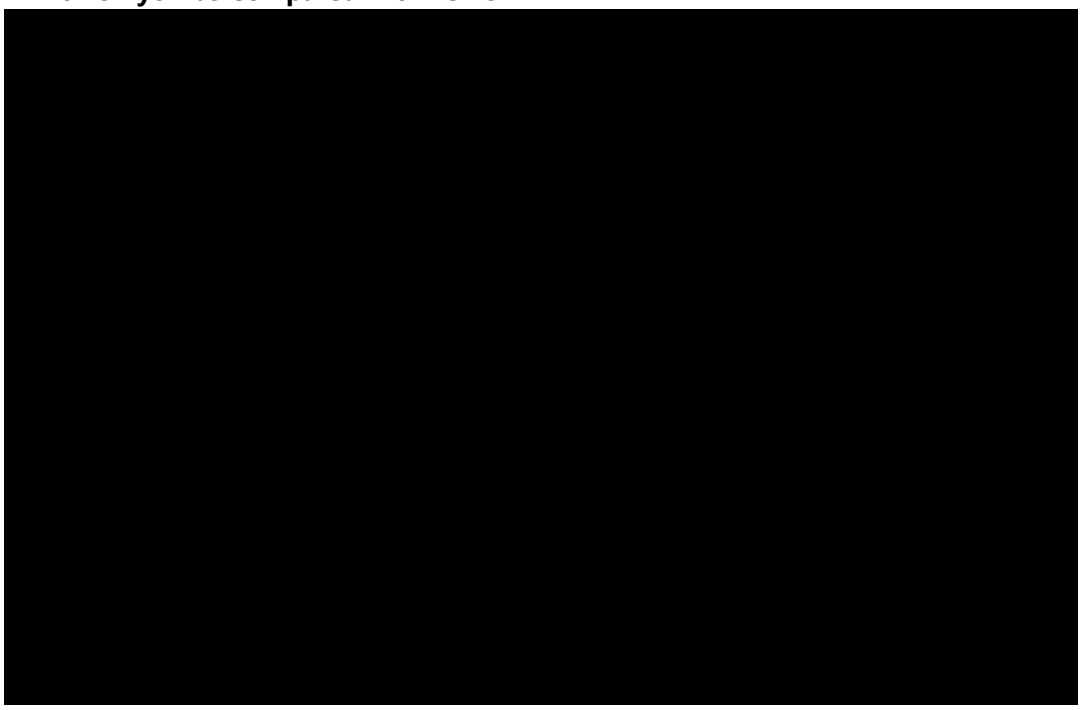
The mean age in the azithromycin group, no antibiotic group and penicillin V was 39.7±13.9, 39.5±13.8 and 42.0±12.8 years respectively.

The risk of death from cardiovascular causes was significantly increased within 5-days of azithromycin treatment compared to no antibiotic use (rate ratio= 2.85, 95% CI 1.13 to 7.24). No significantly increased risk was observed for recent or past use.

As compared with penicillin V, however, azithromycin was not associated with a significantly increased risk in the unadjusted (rate ratio= 0.78, 95% CI 0.47 to 1.28) and after adjustment for propensity scores (rate ratio, 0.93; 95% CI, 0.56 to 1.55). There was no significantly increased risk associated with recent or past use.

In a subgroup analysis that looked at the risk of cardiovascular death based on different baseline characteristics, the risk during current use of azithromycin appeared to be higher among persons with a history of cardiovascular disease than among those without such a history, although the difference was not significant (Table 8). Noting the number of events is numerically small.

Table 8: Subgroup Analyses of the Risk of Death from Cardiovascular Causes with Current Use of Azithromycin as Compared with Penicillin V



Discussion and conclusions

As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of cardiovascular death in young and middle aged adults in Denmark. As compared with penicillin V, however, azithromycin was not associated with a significantly increased risk, indicating that the increased risk that was observed in the comparison with no antibiotic use was entirely attributable to the risk of death associated with acute infection (or some other adverse health characteristic in persons receiving antibiotic treatment, as compared with those not treated with antibiotics) rather than with its treatment.

The findings indicate that the risk of cardiac toxic effects associated with azithromycin as seen from other studies may not be generalisable but may rather be limited to high-risk populations. This study suggests that for the general population of patients seen in office practice, azithromycin can be prescribed without concern about an increased risk of death from cardiovascular causes.

3.1.6 Mortensen et al (2014) – Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia [14]

Aim: this population-based cohort study assessed the association between azithromycin use in patients ≥ 65 years of age hospitalised with pneumonia and outcomes within 90 days of hospital admission, including cardiovascular events (heart failure, myocardial infarction and cardiac arrythmias), and mortality. The study compared patients prescribed azithromycin therapy with patients receiving other guideline-concordant antibiotic therapy.

Methods:

Patients were sourced from the VA Health Care System and included if they were ≥65 years of age hospitalised with pneumonia and received antibiotic treatment during the first 48 hours after hospital admission.

The primary outcomes were 30-day and 90-day mortality, and cardiovascular events (myocardial infarction, heart failure, and cardiac arrhythmia) within 90-days of hospital admission. Prior research has demonstrated that 30-day mortality is largely pneumonia-related while mortality between 30 and 90-days is largely comorbidity-related.

Propensity score matching was used to balance measured confounder between the azithromycin vs no azithromycin. Patients were classified as having used azithromycin if they received at least one dose of azithromycin during the first 48 hours after admission. Odds ratios were calculated to determine the association between azithromycin use and the outcomes using conditional logistic regression models with robust standard errors.

Results: There were 73,690 patients meeting the inclusion criteria. Patients' mean age was 77.8 (95% CI 77.7–77.8) years. Propensity-matched groups were composed of 31,863 azithromycin-exposed and 31,863 matched unexposed.

The 30-day (OR 0.76, 95% CI 0.73–0.80) and 90-day (OR 0.73, 95% CI 0.70–0.76) mortality was significantly lower in those who received azithromycin compared to those who used other antibiotics).

However, there was significant increased odds of myocardial infarctions (5.1% vs. 4.4%, OR 1.17, 95% CI 1.08–1.25) but not for any cardiac event (43.0% vs. 42.7%, OR 1.01, 95% CI 0.98–1.05), cardiac arrhythmias (25.8% vs. 26.0%, OR 0.99, 95% CI 0.95–1.02), or heart failure (26.3% vs. 26.2%, OR 1.01, 95% CI 0.97–1.04).

Discussion and conclusion:

In this national cohort study of veterans hospitalised with pneumonia, treatment with azithromycin was associated with decreased mortality and a slightly increased odds of myocardial infarction compared to no use (use of other antibiotics).

Numerous studies have demonstrated that many patients hospitalised with pneumonia have some type of cardiac event at the time of hospitalisation or soon after. Therefore, it is difficult to differentiate between cardiac events secondary to azithromycin use versus effects of the underlying infection.

Limitations of this study include restricting the population to elderly patients who generally have a higher mortality and baseline cardiovascular risk. Prior to propensity score matching people taking azithromycin did have a smaller but significant difference than unexposed patients. Propensity-score matching was successful in producing two groups with similar characteristics; however it remains possible that unmeasured confounders could bias the results. Finally, there was no data on the duration of azithromycin therapy or specific causes of death.

3.1.7 Sutton et al (2017) – Appraisal of the cardiovascular risks of azithromycin: an observational analysis [15]

Aim: This retrospective observational study assessed the association of cardiovascular mortality in patients prescribed azithromycin compared with patients prescribed alternative antibiotics in an outpatient setting.

Methods:

Using the South Carolina Medicaid claims and pharmacy databases, the study cohort consisted of people aged 17-74 years of age receiving an antibiotic prescription from January 2000 to December 2011.

The study antibiotics included azithromycin, amoxicillin, clindamycin, clarithromycin and 'floxacins' (levofloxacin, ciprofloxacin and moxifloxacin). Given that the unit of analysis was antibiotic course, one person could have multiple antibiotic courses with multiple antibiotics. Participants were excluded if they had been hospitalised within 30 days before receiving the antibiotic or had a high risk of death from causes unrelated to a short-term effect of proarrhythmic medicines.

The primary outcome was cardiovascular death. The date of death and the prescription dispense date were subtracted to get the number of days until cardiovascular death. To create a dependent variable for the multivariate models, cardiovascular death was flagged (yes = 1, no = 0) based on four intervals: 0–5 days, 6–10 days, 0–10 days and 0–30 days. All records that did not have an occurrence of cardiovascular death within the intervals were coded as 0.

This study used both matching and regression adjustment with propensity scores to reduce possible bias in the estimated treatment (group) effect from confounders.

Results:

The total number of prescriptions evaluated in the study include: 283,743 azithromycin, 143,191 amoxicillin, 52,714 clindamycin, 38,133 clarithromycin and 49,734 for the floxacin group.

Non-statistically significant differences in cardiovascular death were observed between the study antibiotics and azithromycin for all time intervals (see Table 9).

- During the 0–5 day interval, all other study antibiotics had lower but not statistically significant odds of cardiac death compared with azithromycin.
- During 6–10 day interval, the odds of cardiac death increased (not statically significant) for amoxicillin, clarithromycin and clindamycin.
- Estimates for the 0–10 day and 0–30 day timeframe revealed non-statistically significant differences between azithromycin and all study antibiotics.

Table 9: Cardiovascular deaths: inverse probability treatment weighting adjusted pooled logistic regression models

Discussion and conclusions:

The mortality rates for azithromycin users versus other study antibiotics were not significantly different at any time interval in patients at a low risk of death from other causes than study antibiotics.

Compared to the study by Ray et al (see section 3.1.2), this study did not find an association between azithromycin and cardiovascular death. One important difference is that Ray et al evaluated an older cohort (ages 30–74 years) whereas the author's cohort evaluated a wider range (ages 17–74 years). It is possible that the cardiovascular risk associated with azithromycin found by Ray et al is specific to an older age group.

This study suggests that cardiovascular mortality association azithromycin seen in previous studies may not be applicable to the general population (ie, not at risk) and that further research is needed to define the population at greatest risk.

3.1.8 Chou et al (2014) – Risks of Cardiac Arrhythmia and Mortality Among Patients Using New-Generation Macrolides, Fluoroquinolones, and β-Lactam/β-Lactamase Inhibitors: A Taiwanese Nationwide Study [16]

Aim: A nationwide, population-based study was carried out to compare cardiovascular outcomes among users of several commonly prescribed macrolides (azithromycin, clarithromycin), fluroquinolones and amoxicillin clavulanic acid.

Methods:

The Taiwan National Health Insurance Database was used to compare the risk of ventricular arrythmia and cardiovascular death among patients using the above oral antibiotics between the years 2001 and 2011. The date of first prescription of study antibiotics was defined as the index date.

The primary outcome was severe ventricular arrhythmia, defined by the inpatient or outpatient (including emergency department visit) diagnosis of ventricular arrhythmia, sudden death, sudden cardiac arrest, or cardiopulmonary resuscitation, plus any prescription for antiarrhythmic agents (including amiodarone, lidocaine, magnesium, or sotalol). The secondary outcomes were cardiovascular death and the composite outcome of ventricular arrhythmia or cardiovascular death.

A logistic regression model adjusted for propensity score was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for adverse cardiac outcomes occurring within 7 days after the initiation of antibiotic treatment.

Results:

A total of 1,102,358 users of amoxicillin-clavulanate, 66 745 users of azithromycin, 393 243 users of clarithromycin, 205 205 users of ciprofloxacin, 117 352 users of levofloxacin, and 38 833 users of moxifloxacin were included in the analysis.

The use of azithromycin and moxifloxacin was associated with significant increases in the risks of ventricular arrhythmia and cardiovascular death compared with amoxicillin-clavulanate treatment.

The use of levofloxacin was associated with a significant increase in the risk of cardiovascular death compared with amoxicillin-clavulanate treatment.

The adjusted OR (aOR) for ventricular arrhythmia was 4.32 (95% CI, 2.95–6.33) for azithromycin, 3.30 (95% CI, 2.07–5.25) for moxifloxacin, and 1.41 (95% CI, .91–2.18) for levofloxacin.

For cardiovascular death, the aORs for azithromycin, moxifloxacin, and levofloxacin were 2.62 (95% CI, 1.69–4.06), 2.31 (95% CI, 1.39–3.84), and 1.77 (95% CI, 1.22–2.59), respectively. Neither clarithromycin nor ciprofloxacin demonstrated a significant association with ventricular arrhythmia nor cardiovascular death.

Discussion and conclusions:

Azithromycin and moxifloxacin had 2- to 6-fold increased risks of ventricular arrhythmia and cardiovascular death compared with amoxicillin-clavulanate. Among newer macrolides, azithromycin was associated with a higher risk of adverse cardiovascular outcome than clarithromycin. Despite the significantly increased relative risks associated with these antibiotics, the absolute risks were very small, especially in patients without underlying cardiovascular disease. In patients with underlying cardiovascular disease, the absolute risk of cardiovascular death per 1000 individuals was 1.45 for azithromycin and 1.02 for moxifloxacin, which had a 2- to 3-fold increased risk compared with amoxicillin-clavulanate use. Additional research is needed to determine whether these increased risks are due to the medicines or related to the severity of infection or the pathogens themselves.

3.1.9 DerSarkissian et al (2022) – The acute effects of azithromycin use on cardiovascular mortality as compared with amoxicillin–clavulanate in US Veterans [17]

Aim: To assess cardiovascular and non-cardiovascular mortality associated with azithromycin versus amoxicillin–clavulanate among US Veterans who received these antibiotics for a respiratory or ENT infection.

Methods:

Electronic health record data from the US Veterans Health Administration database were used to identify Veterans (30–74 years) with outpatient dispensings of oral azithromycin versus amoxicillin–clavulanate for respiratory or ear–nose– throat infection between the years 2000 to 2014.

Outcomes assessed were risk of cardiovascular death and non-cardiovascular death within 1–5 and 6–10 days post-dispensing. Inverse probability of treatment-weighted proportional hazards models and binomial regression models were used to estimate hazard ratios (HRs).

High-risk subgroups were examined in stratified analyses: (1) patients with a history of cardiovascular disease, defined as an inpatient or outpatient encounter with indicators of cardiovascular disease ≤1 year prior to the index antibiotic dispensing (2) patients in the top decile of cardiovascular mortality risk score.

Results:

There were 629,345 azithromycin and 168,429 amoxicillin–clavulanate dispensings for respiratory indications, 143,783 azithromycin, and 203,142 amoxicillin–clavulanate dispensings for ear–nose–throat indications. The mean patient age was 55 years.

Among dispensings for respiratory indications, azithromycin was not associated with a significant risk of cardiovascular death during days 1–5 (HR= 1.12, 95% CI 0.63 to 2.00) and days 6–10 (HR= 0.65, 95% CI 0.36 to 1.16). Similarly, no elevation in risk for azithromycin vs. amoxicillin–clavulanate users was found for ENT indications during days 1–5 (HR= 0.46, 95% CI 0.09 to 2.30) and days 6–10 (HR= 0.70, 95% CI 0.22 to 2.29).

After pooling results across indications, the HR for the risk of cardiovascular death associated with azithromycin versus amoxicillin– clavulanate was 1.00 (95% CI 0.55 to 1.81) during days 1–5 and 0.66 (95% CI 0.39 to 1.11) during days 6–10. Similar results were found for the risk of non-cardiovascular death.

Results were no different in subgroups of patients at high risk of cardiovascular death, and when assessing cardiac death or non-cardiovascular death.

Discussion and conclusions:

Azithromycin was not associated with an elevated risk of cardiovascular, non-cardiovascular, or cardiac death relative to amoxicillin– clavulanate among US Veterans treated for non-ENT respiratory or ENT indications.

This differed from earlier studies by Ray et al, Zaroff et al and Rao et al. The difference may be due to the previous authors being unable to fully adjust for confounding by indication as about a third of indication data in each study were missing.

3.1.10 Bin Abdulhak et al (2015) – Azithromycin and risk of cardiovascular death: a meta-analytic review of observational studies [18]

Aim: a systematic review of the literature and meta-analysis was performed to examine the effect of azithromycin on all-cause mortality and cardiovascular death.

Methods: literature review from 1990 to 2014 from Ovid MEDLINE. Studies that assessed the effect of azithromycin as a primary outcome on all-cause mortality or cardiovascular death were considered for inclusion.

The Newcastle–Ottawa quality assessment scale (NOS) was used to evaluate the quality of observational studies.

Inverse variance method meta-analysis was used to pool studies' rate ratio, odds ratio, or hazards ratio (HR) into random effects model meta-analysis. The outcome of interest was risk of death (related to cardiovascular and/or non-cardiovascular causes) with the use of azithromycin (defined as within 1–10 days of therapy) as reported from individual studies in comparison with other antibiotics.

Sensitivity analyses was carried out by stratifying risk of death with azithromycin use among younger (mean age <40 years) and older populations (mean age ≥40 years) separately, including risk of death with current use of azithromycin (defined as within 1–5 days of start of therapy) and risk of death with recent use of azithromycin (from 6 to 10 days of therapy) among all included studies and stratified by age group.

HR, with its 95% confidence interval (CI), was used to calculate the overall effect estimate. Heterogeneity among included studies was assessed using x^2 and I^2 tests.

Results:

Five observational studies, including 2,246,178 episodes of azithromycin use met the inclusion criteria. Out of the five studies, there were eight results for the primary outcome included in the meta-analysis.

Azithromycin use within 1-10 days was not associated with a statistically significant increased risk of death from any cause (HR =0.99, 95% CI 0.82 to 1.19, I^2=54, or cardiovascular cause (Figure 4) or from cardiovascular causes (HR=1.15, 95% CI 0.66 to 2.00, I^2=64%) (Figure 5). A moderate degree of between-study heterogeneity and possible publication bias was noted.

Figure 4: Random effects model meta-analysis of risk of death from any cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI

Figure 5: Random effects model meta-analysis of risk of death from cardiovascular cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI

In the subgroup analysis, azithromycin use in younger population was not associated with an increased risk of death (from any cause) (HR= 0.85, 95% CI 0.66–1.09, I=0%). However, current use of azithromycin (within 1–5 days of therapy) was associated with a higher risk of death among older population (> 40 years of age) with mild degree of heterogeneity (HR= 1.64, 95% CI 1.23–2.19, I=4%).

Discussion and conclusions:

There was no overall increased risk of all-cause mortality or cardiovascular death with azithromycin use in comparison with other antibiotics, however a moderate degree of between-study heterogeneity was noted.

Subgroup analyses showed that current azithromycin use (within 1–5 days of therapy) was associated with a higher risk of death in older populations (40 years or older) and with only a mild degree of between-study heterogeneity.

The observed higher rate of death in association with current azithromycin use in an older population as suggested by the study's subgroup analysis may be a result of proarrhythmic properties of the drug. However, it might also be related to the specific characteristics of the population under study: older, higher rate of comorbidities, higher baseline risk of death and cardiovascular events, confounding by indications, and the presence of residual unmeasured confounders that could have biased the result toward such association.

Comments on literature review for azithromycin and cardiovascular death:
Overall, there is a substantial number of observational studies looking at the association between azithromycin and cardiovascular death. This may be due to the wide use of this macrolide overseas. Observational studies show mixed data on an increased risk of cardiovascular death which may be explained by general limitations of cohort studies (eg, confounding by indication), missing data and differences in dataset/source population used in each study.

Literature review for other macrolides

3.1.11 Inghammar et al (2018) – Long-term risk of cardiovascular death with the use of clarithromycin and roxithromycin: a nationwide cohort study [19]

Aim: To assess whether use of clarithromycin or roxithromycin was associated with an increased long-term risk of cardiovascular death compared with penicillin V (an antibiotic without known cardiovascular side effects).

Methods: The study population was a historical cohort among Danish adults aged 40 to 74 years who received an outpatient prescription for clarithromycin, roxithromycin or penicillin V between 1997 and 2011.

The main outcome was cardiovascular death, defined by one of the following ICD-10 codes: ischemic heart disease; arrhythmic disorders, cardiac arrest, or heart failure; cerebral infarction or atherosclerosis. The rate ratio for cardiovascular death was estimated with the use of clarithromycin or roxithromycin, compared with the use of penicillin V, using Poisson regression. In secondary analyses, time of follow-up was subdivided into 0–7 days (representing "current use"), 8–89 days, or 90–364 days from start of treatment.

To reduce the potential for confounding from baseline characteristics at the start of treatment, courses of clarithromycin and penicillin V and, separately, roxithromycin and penicillin V were matched 1:4 on the propensity score, yielding two separate, matched study cohorts, one for each macrolide. The risk associated with the study macrolide was also assessed according to time after treatment start and according to subgroups of age, sex, and underlying cardiac disease as estimated by a cardiovascular risk score.

Results: From a source population of 3,380,262 Danish adults, the cohort used for the analyses of roxithromycin versus penicillin V included 698,899 courses of roxithromycin and 2,721,538 courses of penicillin V. The cohort used for the analyses of clarithromycin versus penicillin V consisted of 187,887 courses of clarithromycin and 751,543 courses of penicillin V. For clarithromycin use, 29,310 individuals contributed more than one antibiotic course, and for roxithromycin use, 129,976 contributed more than one course.

Table 10 shows the incidence rate of cardiovascular death for each group and the rate ratio. There was no statistically increased risk of cardiovascular death from use of clarithromycin or roxithromycin compared to penicillin V. In addition, there were no differences across subgroups of age (p=0.82) or across different cardiac risk scores (p=0.52).

Table 10: Risk of Cardiovascular Death Associated with Use of Clarithromycin or Roxithromycin Compared With Penicillin V, During 1 Year and According to Time After Treatment Start, Denmark, 1997–2011

Discussion and conclusions: The results of this large population-based cohort study do not support the presence of a long-term risk of cardiovascular death associated with administration of clarithromycin or roxithromycin as compared with penicillin V. The authors noted limitations of this study included lack of information on important risk factors for cardiovascular death such as smoking and BMI and the lack of information on indication for antibiotic treatment.

3.1.12 Svanstrom et al (2014) – Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study [20]

Aim: A nationwide registry-based cohort study was carried out in Denmark to investigate the risk of cardiac death associated with clarithromycin and roxithromycin, compared to pencilling V.

Methods:

The cohort comprised of people in the Danish Civil Registration System, aged 40-74 years.

The primary study outcome was cardiac death associated with the use of clarithromycin and roxithromycin, compared with penicillin V. In subgroup analyses, the risk of cardiac death with use in subgroups according to sex, age, an empirically derived risk score for cardiac death, and concomitant use of cytochrome P450 3A inhibiting drugs were assessed. Using Poisson regression, rate ratios were estimated comparing individual macrolides with penicillin V during time periods of current use (0-7 days from start of treatment) and past use (8-37 days).

Confounding by indication was minimised by using penicillin V as the comparator, an antibiotic used similarly to the study antibiotics. To further reduce the potential for confounding and to increase the likelihood of isolating an effect attributable to the previously hypothesised pro-arrhythmic mechanism, participants with serious disease, who may be at high baseline risk of death from non-cardiac causes were excluded. Thirdly, to account for baseline differences in the risk of cardiac death, propensity score matching was carried out to incorporate a wide range of potential confounders.

Results: From a source population of 3,379,788 people, the study cohort consisted of 160,297 prescriptions for clarithromycin, 588,988 prescriptions for roxithromycin, and 4,355,309 prescriptions for penicillin V.

Among a total of 285 cardiac deaths observed during current use of the study drugs, 18 occurred during use of clarithromycin (incidence rate 5.3 per 1000 person years), 32 during use of roxithromycin (2.5 per 1000 person years), and 235 during use of penicillin V (2.5 per 1000 person years).

In unadjusted analysis, current use of clarithromycin was associated with a significantly increased risk of cardiac death (rate ratio 2.07, 95% CI 1.28 to 3.35); this association persisted after propensity score adjustment (1.76, 1.08 to 2.85). The adjusted absolute risk difference for current use of clarithromycin, compared with use of penicillin V, was 37 (95% CI 4 to 90) cardiac deaths per 1 million treatment courses. With regard to past use, clarithromycin was not associated with an increased risk of cardiac death.

Current use of roxithromycin was not associated with an increased risk of cardiac death in adjusted analysis (rate ratio 1.04, 0.72 to 1.51). Compared with penicillin V, the adjusted absolute risk difference for current use of roxithromycin was 2 (–14 to 25) cardiac deaths per 1 million courses. There was no increased risk of cardiac death with past use of roxithromycin in either unadjusted or adjusted analysis.

In the sensitivity analysis, *current use* of clarithromycin was associated with an increased risk of cardiac death (1.63, 95% CI 0.87 to 3.03), while there was no increased risk with roxithromycin (0.92, 95% CI 0.60 to 1.39).

In the sub-group analysis, there were no statistically significant difference in the risk of cardiovascular death based on age, concomitant use of a CYP 3A4 inhibitor, or a person's cardiac risk score. There was an increased risk of cardiovascular death with clarithromycin among women.

Discussion and conclusions: There was a significantly increased risk of cardiac death associated with current use of clarithromycin but not roxithromycin, compared to penicillin V. However, the absolute risk was very small.

The observed association with clarithromycin seemed to be largely attributable to women. This finding is consistent with female sex being a known risk factor for drug induced cardiac arrhythmia in general and macrolide induced arrhythmia in particular.

Available mechanistic data comparing individual macrolides suggest that clarithromycin has higher potency of I_{Kr} inhibition compared with roxithromycin. If true, the observed increased risk with clarithromycin but not roxithromycin may represent a clinical manifestation of these differing pharmacodynamic properties.

3.1.13 Wong et al (2016) – Cardiovascular outcomes associated with use of clarithromycin: population based study [21]

Aim: To investigate whether clarithromycin was associated with cardiovascular outcomes among the general population in Hong Kong.

Methods: Using the Hong Kong Hospital Authority database consisting of a population of 7 million, the cohort consisted of patients aged 18 years and older that were prescribed either oral clarithromycin or amoxicillin between 2005 and 2009 for *H. pylori* eradication. The observation period commenced from the date of the first antibiotic prescription (index date) and ended at the earliest occurrence of the outcome, death, subsequent use of clarithromycin or amoxicillin, or end of study.

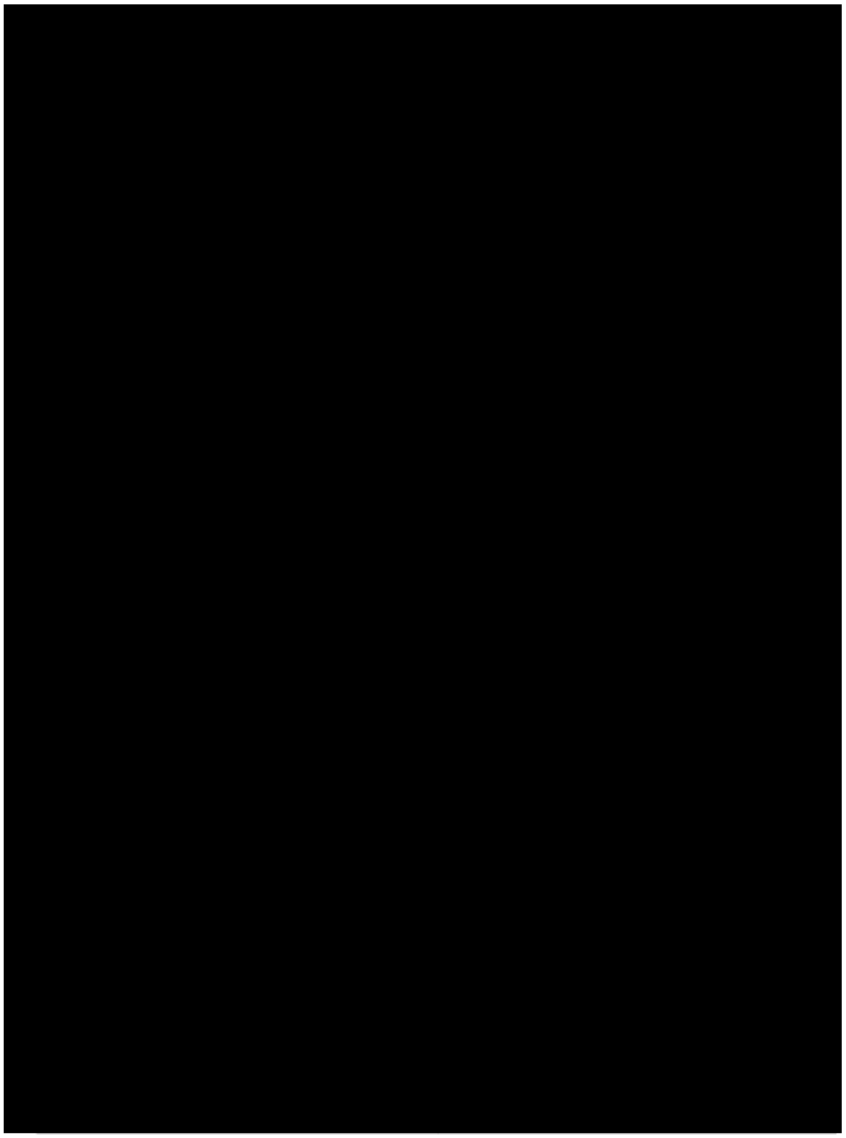
All-cause, cardiac and non-cardiac mortality were secondary endpoints.

After initial adjustment for age, sex, and history of the event of interest, Poisson regression was used to estimate the rate ratios for clarithromycin users compared with amoxicillin users during current (days 1-14), recent (days 15-30), and past use (31 days +). To control for confounding, propensity score adjustment was utilised.

Results: The study cohort consisted of 108,990 prescriptions for clarithromycin and 217,793 prescriptions for amoxicillin.

The risk of cardiac mortality was higher with current use of clarithromycin compared to amoxicillin (rate ratio 1.93, 95% CI 1.61 to 2.30), following propensity score adjustment, the association (rate ratio 1.67, 95% CI 1.36 to 2.06) (Figure 6).

Figure 6: Propensity score adjusted rate ratios for all outcomes with clarithromycin use compared with amoxicillin use



Subgroup analysis showed that rate ratio for cardiac death were comparable between men and women. The rate of cardiac mortality was 118.7 per 1000 person years in patients aged 75 or more receiving amoxicillin, considerably higher than that of patients aged 40-74 receiving amoxicillin (12.9 per 1000 person years). In addition, absolute risk differences of cardiac death were also higher among patients with hypertensive diseases or diabetes mellitus.

Discussion and conclusions: There was no increased risk of cardiovascular outcomes observed with long term clarithromycin treatment compared with amoxicillin treatment but there was a suggestion of an increased cardiovascular risk during and immediately after clarithromycin use. The risk was more pronounced with older age and among patients with hypertension or diabetes.

3.1.14 You et al (2019) – Clarithromycin use and the risk of mortality and cardiovascular events: A systematic review and meta-analysis [22]

Aim: Epidemiological studies using multivariate models regarding the cardiovascular risks associated with clarithromycin use remained controversial because of different study designs and follow-up durations. The aim of this systematic review and meta-analysis is to summarise the association between clarithromycin use and the short and long-term all cause and cardiovascular mortality in different study populations.

Methods: A literature search up to 31 December 2018 was conducted using PubMed, Embase, Web of Science and Cochrane. Studies containing the following information were included: (1) exposure with clarithromycin treatment versus either comparative antibiotics or placebo; (2) mortality or cardiovascular events as the outcome of interests; and (3) adult populations (≥ 18 years).

All-cause mortality was considered the primary outcome of interest because it is the most commonly reported endpoint. Acute myocardial infarction, cardiac mortality, and arrhythmia were considered as secondary outcomes.

Follow-up duration was determined between the first date of antibiotic prescription and occurrence of outcome or censoring. The follow-up durations of the studies that met the inclusion criteria ranged from 5 days to 3 months, or 1 to 3 years. Thus, the authors divided the follow-up time into short-term (<3 months) and long-term (≥ 1 year). The immediate follow-up duration was defined as ≤ 2 weeks, since clarithromycin was rarely used for more than 2 weeks.

Random effects models were chosen a *priori* to calculate summary effect estimates, weighting for inverse variance separately for RCTs and observational studies. The rate ratio was used as the main pooled effect estimates.

Results: The meta-analysis included three RCTs and ten observational studies with a total of 8,351,815 subjects (1,124,672 cases and 7,227,143 controls). Only results relating to cardiac mortality will be presented here.

Five observational studies were included in the analysis on cardiac mortality.

There was not an increased risk of cardiac mortality with the use of clarithromycin short term (≤ 3 months) compared to other antibiotics (pooled RR from observational studies= 1.03, 95% CI = 0.53 to 2.01) (Figure 7, Panel A). Additionally, in the subgroup analysis, clarithromycin use was not associated with an immediate risk (≤ 2 weeks) of cardiac mortality (pooled RR = 1.19, 95% CI = 0.69–2.07) (Figure 7, Panel B). Large heterogeneity was noted.

Figure 7: Pooled risk ratios for (A) cardiac mortality in observational studies with short term (≤ 3 months) follow up, and (B) cardiac mortality with immediate (≤ 2 weeks) follow up

Discussion and conclusions: There was no significant increased risk of cardiac mortality comparing clarithromycin use versus alternative antibiotics use or placebo with a ≤ 3 months and ≤ 2 weeks follow up.

3.1.15 Ray et al (2004) – Oral erythromycin and the risk of sudden death from cardiac causes [23]

Aim: To study the association between use of erythromycin and the risk of sudden death from cardiac causes (usually as a result of ventricular tachyarrhythmia), and whether this risk was increased with the concurrent use of strong CYP 3A4 inhibitors.

Methods: The study cohort consisted of Tennessee Medicaid enrolees who had been identified for previous investigations of sudden death from cardiac causes.

To be eligible for cohort inclusion, the person had to be between 15 to 84 years of age and receiving a prescription for erythromycin or amoxicillin, could not be residing in a long-term care facility and could not have life-threatening non-cardiac illness.

Every person-day of follow-up was classified according to the study medicine used and the type of use. Current use was defined according to days of supply from the day the prescription was filled. Non-use of a medicine was defined as no use within the previous 365 days. Former use was defined as some use of a study medicine that was not current but had occurred within the previous 365 days.

The outcome was sudden death from cardiac causes occurring in a community setting. Sudden death from cardiac causes was defined as a sudden pulseless condition that was fatal (within 48 hours) and that was consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death. Death from different cardiac causes such as heart failure or bradyarrhythmia was excluded.

Multivariate incidence-rate ratios and 95% CI were estimated with the use of Poisson regression models.

Results:

The study cohort included 1,249,943 person-years of follow-up. The mean age among members of the cohort was 45 years; 25% of the subjects were 65 years of age or older.

A total of 5305 person-years of current use of erythromycin were included and 111,779 person-years of former use, as well as 6846 person-years of current use of amoxicillin and 1,126,013 person-years who had not used any antibiotics.

The rate of sudden death from cardiac causes was twice as high among current users of erythromycin (incidence-rate ratio= 2.01; 95% CI 1.08 to 3.75, p=0.03) (Table 11) as among those who did not use any of the study antibiotics. In contrast, there was no significant increase in the risk of sudden death among former users of erythromycin (incidence rate ratio= 0.89; 95% CI, 0.72 to 1.09, p=0.26) or current users of amoxicillin (incidence rate ratio= 1.18; 95% CI 0.59 to 2.36, p=0.65).

Table 11: Incidence-Rate Ratio for Sudden Death from Cardiac Causes, According to Antibiotic Use*

There was a marked increase in the risk of sudden death from cardiac causes among current users of CYP3A4 inhibitors and erythromycin (incident risk-ratio= 5.35, 95% CI 1.72 to 16.64). There was no increase in the risk among those who concurrently used amoxicillin and CYP3A inhibitors or those currently using any of the study antibiotic medicines who had formerly used CYP3A inhibitors.

Discussion and conclusions:

The rate of sudden death from cardiac causes was twice as high among patients who were current users of oral erythromycin as among those who had not used any of the study antibiotic drugs. In contrast, those who had formerly used erythromycin or were currently using amoxicillin had no significant increase in risk. A key finding was that the risk was greatest among those concomitantly using erythromycin and the study drugs that were likely to inhibit its metabolism. Among such patients, the risk of sudden death from cardiac causes was five times as high as that among those who were not using any of the study antibiotic drugs or CYP3A inhibitors.

The study provided no direct data with regard to the mechanisms by which the concomitant use of erythromycin and the study CYP3A inhibitors increased the risk of sudden death from cardiac causes. The most probable explanation is that the concurrent use resulted in an increase in the plasma erythromycin concentrations, thereby increasing the risk of QT prolongation (a known, dose-associated effect of erythromycin) and thus of serious ventricular arrhythmias.

Comment
This study looked at cardiovascular death where the cause was only from ventricular tachyarrhythmias.

Comments on literature review for other macrolides and cardiovascular death:
The literature review showed there may be an increased risk of cardiovascular death with clarithromycin and erythromycin. There does not appear to be a risk with roxithromycin.

Meta-analysis on macrolides as a class

3.1.16 Wu et al (2023) – Administration of macrolide antibiotics increases cardiovascular risk [24]

Aim: To conduct a meta-analysis looking at the association between macrolides and cardiovascular disease risk.

Methods: Literature articles were searched on Medline, EMBASE, and ClinicalTrials.gov up to 31 August 2022. Articles were included if they were cohort and case-control studies or RCTs that reported the association between macrolides and the risk of cardiovascular events.

The outcome was ventricular arrythmia or sudden cardiac death (VA/SCD), MI, cardiovascular disease death and all-cause death. VA/SCD death was defined according to the ICD-10 as ventricular tachycardia, TdP, ventricular fibrillation, ventricular flutter, sudden cardiac arrest, and SCD.

The random-effects model was used with a RR calculated with 95% CI. Heterogenicity was assessed using I^2.

"Time of exposure to macrolides" was defined as: current referred to the patient's current use of macrolides, recent was defined as use of macrolides within one month, and former involved the use of macrolides within one year. A subgroup analysis was performed on the timing of macrolide use and cardiovascular risk.

A subgroup analysis was also performed looking at the association between different types of macrolides and cardiovascular risk.

Results: Eighty studies were included in the meta-analysis (42 cohort, 23 RCT and 15 case-control) encompassing 39,374,874 patients.

Only the analysis relating to SCD and cardiovascular death is outlined below:

Compared with the non-macrolide treatment group, macrolides were associated with a higher risk of VA/SCD (RR: 1.53, 95% CI: 1.34–1.76, I^2 = 49.9%).

Nineteen studies consisting of 24,181,047 patients reported cardiovascular death. Compared with non-macrolide treatment group, macrolides were associated with higher cardiovascular death (RR: 1.34, 95% CI: 1.14–1.58, I^2 = 75.2%). A random-effects model was applied due to the high heterogeneity. No funnel plot asymmetry was observed. Moreover, neither Egger's test nor Begg's test showed any publication bias (Begg test, p=0.58; Egger test, p=0.71).

The subgroup analysis of the association between different types of macrolides and cardiovascular death is outlined in Table 12. There was an increased risk of cardiovascular death from the use of azithromycin. No association for an increased risk of cardiovascular death was observed with clarithromycin and roxithromycin. For erythromycin, there was insufficient information studies to perform a subgroup analysis.

Table 12: Summary of individual drug and timing of macrolides use in subgroup analysis

Subgroup analysis on the timing of macrolides showed that the risk of VA/SCD was increased with *current* and *recent* use of macrolides. There was an increased risk of cardiovascular death with *current* use of macrolides (Table 12 above).

Discussion and conclusions: Macrolide use increases the risk of cardiovascular death, VA/SCD. Both azithromycin and clarithromycin increase the incidence of VA/SCD, and azithromycin tends to increase the risk of cardiovascular death. Current use of macrolide was associated with an increased risk of VA/SCD and cardiovascular death.

Only azithromycin was significantly associated with an increased risk of cardiovascular death among the four macrolides since azithromycin increased not only the risk of myocardial infarction but also the risk of ventricular arrythmias or sudden cardiac death.

3.1.17 Cheng et al (2015) – The role of macrolide antibiotics in increasing cardiovascular risk [4]

Aim: This meta-analysis examined the link between oral macrolide use and the risk of sudden cardiac death or ventricular tachyarrhythmias (SCD/VTA), cardiovascular death, and death from any cause.

Methods: Literature articles were searched on Medline and EMBASE up to 30 April 2015.

The primary study endpoint was SCA/VTA, as defined by ICD-10: ventricular tachycardia, TdP, ventricular fibrillation, ventricular flutter, sudden cardiac arrest, and SCD. The secondary endpoint was CV death, as it was hypothesised that the incidence of cardiac death should be increased if macrolides were pro-arrhythmic.

Relative risk (RR) was used as a measurement of the association between macrolides and cardiovascular risk. For case-control studies, the odds ratio (OR) was used as estimates of the RR because cardiovascular events are sufficiently rare.

Results (all-cause mortality not discussed below):

Sudden cardiac death or ventricular tachyarrhythmias

11 studies were included for this outcome comprising of 6,639,411 individuals and 5,810 events. Patients taking macrolides had a significantly increased risk for developing SCD/VTA compared to those not on macrolide therapy (RR= 2.42, 95% CI 1.60 to 3.63, p <0.001). There was high heterogenicity of the RRs across the studies with a I^2=85.42%, 95% CI 75.65 to 91.27%, p<0.001). When the analysis was confined to those studies with propensity-matched cohorts, the overall combined RR did not materially change, but no evidence of significant heterogeneity was observed among the remaining studies. Neither funnel plots nor Egger and Begg test results showed evidence of publication bias (Egger test: p= 0.44; Begg test: p =0.11).

Cardiovascular mortality

Twelve studies were included for the outcome of cardiovascular death, consisting of 17,060,440 individuals and 4,199 events. Use of macrolide was associated with an increased risk of cardiovascular death (RR=1.31, 95% CI 1.06 to 1.62, p=0.01) with moderate between-study heterogeneity (I^2= 64.8%; 95% CI: 34.84% to 80.99%, p= 0.001).

Risk estimates did not materially change after analyses with fixed-effect models, inclusion of the studies with populations >10,000 and with propensity-matched cohort, or exclusion of the largest study and 1 outlier study, with moderate-to-high heterogeneity across studies (Egger test, p= 0.94; Begg test, p= 0.10).

Stratified analysis:

Stratified analysis was carried out for various factors such as individual macrolides, age, sex, current/former macrolide use and adjustment of cardiovascular risk factors (Table 13).

There was an increased risk of SCD/VTA with current use of azithromycin, erythromycin, and clarithromycin. A stronger association between macrolide and SCA/VTA was noted when adjusted for cardiovascular risk factors.

For cardiovascular mortality, an association was found with the use of azithromycin and clarithromycin, current use of macrolides, and after adjustment for cardiovascular risk factors.

Table 13: Stratified analysis and heterogeneity of RRs of sudden cardiac death or ventricular tachyarrhythmias, cardiovascular death, and death from any cause

The absolute risk from the use of macrolides was estimated to be 36.6 SCD and 38.2 cardiac deaths per 1 million courses.

Discussion and conclusions:

There was a significantly increased risk of SCD/VTA and cardiovascular death with current use of macrolides. In stratified analysis, azithromycin, clarithromycin, and erythromycin were associated with increased risk of SCD/VTA, and azithromycin and clarithromycin with increased risk of cardiovascular death.

The estimates for additional SCD and cardiac deaths per 1 million treatment courses were remarkably close, suggesting that most ventricular tachyarrhythmia observed in the macrolide groups might not result in fatal outcomes. The absolute risks for sudden cardiac death and cardiac death are small, so this finding will probably have limited effect on prescribing practice in individual patients.

This meta-analysis suggests that the association between macrolide use and cardiovascular risk may be largely mediated by an acute toxic mechanism, supported by the higher risk observed with current use of macrolides (compared to former use) and that ventricular arrhythmias occurred mainly during short-term therapy.

Blockage of the I_{kr} encoded by human ether-a-go-go-related gene (HERG), prolongation of the QT interval, and thus increased risk of ventricular tachyarrhythmias are thought to be the underlying mechanisms for acute cardiac toxicity with macrolides. Available mechanistic data comparing individual macrolides suggest that clarithromycin and erythromycin have higher potency of I_{kr} inhibition compared with roxithromycin, and thus higher potential for QT prolongation and proarrhythmic properties. Although azithromycin has been considered the safest of the macrolides, because of the lack of CYP interaction, and shows the weakest blockade of I_{kr} in vitro, this study suggests that azithromycin might increase sudden cardiac death risk similar

to clarithromycin and erythromycin. Therefore, the *in vitro* data about azithromycin's pharmacodynamic property might not truly reflect how it works *in vivo*.

3.1.18 Li et al (2016) – Association of macrolides with overall mortality and cardiac death among patients with various infections: A meta-analysis [25]

Aim: To assess the risks and benefits of macrolide therapy by systematically reviewing studies on macrolide use and cardiac death and mortality among patients hospitalised with various infections.

Methods: A search of published literature from Medline, Pubmed, Cochrane library and Embase was conducted up to May 2015. Studies were included if they were a case-control study or cohort study, and if they investigated the association between macrolides and the risk of cardiac death/all-cause death.

The significance of the combined odds ratio (OR) was determined by the Z-test, in which $p<0.05$ was considered significant. The χ^2-based Q statistical test was used for the assessment of the between-study heterogeneity, which was considered significant for $P<0.1$. In analyses, if the heterogeneity was low (<50%), a fixed-effect model, or else applied the random-effect model was used.

Results: This meta-analysis included 10 studies. Only cardiovascular mortality is discussed below.

Use of macrolides was not significantly associated with cardiac death (OR=1.43, 95% CI 0.86 to 2.40). There was high heterogeneity (I^2=87%) (Figure 8, Panel A).

In previous studies, roxithromycin was not found to be associated with cardiovascular death, therefore the authors restricted the analysis to clarithromycin and azithromycin (there were no studies on erythromycin). This showed an increased risk of cardiac death in a population of older individuals (aged >48 years) with a OR=1.99 (95% CI, 1.53 to 2.49), with a I^2=37% (Figure 8, Panel B).

Figure 8: Intervention effect of macrolides versus non-macrolides on cardiac death. Panel (A) Macrolide treatment versus non-macrolide therapy and cardiac death in patients of all age groups. Panel (B) Association of macrolides with cardiac death among elder patients (average age >45 years).

Discussion and conclusions: Macrolide use was associated with significant increase in the risk of cardiac death in patients over 48 years of age. This increased risk was probably caused by its proarrhythmic effect. The finding was consistent with previous studies.

The authors discuss two US cohort studies: one found an increased risk of cardiovascular death associated with macrolide use among patients with high baseline risk of cardiovascular diseases while the other found no increased risk of cardiac death associated with macrolide use in a general population of young and middle-aged adults. This finding suggests that macrolides influenced cardiovascular mortality in a selected population.

3.2 International review and action

This section relates specifically to cardiovascular mortality rather than QT prolongation/ventricular arrythmias.

3.2.1 US Food and Drug Administration

Clarithromycin and potential increased risk of heart problems (2018) [26]

In 2018, the FDA issued a drug safety announcement advising healthcare professionals to be cautious prescribing clarithromycin to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later.

The large clinical trial, called the CLARICOR trial, observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin that became apparent after patients had been followed for one year or longer. There is no clear explanation for how clarithromycin would lead to more deaths than placebo. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. All the studies had limitations in how they were designed. Of the six observational studies published to date in patients with or without coronary artery disease, two found evidence of long-term risks from clarithromycin, and four did not. Overall, results from the prospective, placebo controlled CLARICOR trial provide the strongest evidence of the increase in risk compared to the observational study results. Based on these studies, the FDA was unable to determine why the risk of death is greater for patients with heart disease.

The FDA has added the study results to the clarithromycin labelling.

Azithromycin and cardiovascular death (2021) [27]

In 2021, the US azithromycin labelling was updated to include cardiovascular death in the 'warnings and precautions' and 'adverse reactions' section, based on information from the published literature and observational studies.

3.2.2 Therapeutics Goods Administration (Australia)

Azithromycin and cardiovascular death (2024) [27, 28]

The TGA have received 4 reports possibly associating azithromycin with cardiovascular death (to March 2024). The reports involved patients of both genders ranging in age from 26 to 84, with the majority aged over 60 years. In 2 of these cases, azithromycin was the only suspect medication.

In 2023, the TGA sought advice from their Advisory Committee on Medicines (ACM) on the evidence associated with the signal of azithromycin and cardiovascular death and whether the term 'cardiovascular death' should be added to the Australian Product Information (PI).

At the time, the Australian PI for azithromycin did not list the term 'cardiovascular death' but included ventricular arrhythmias associated with prolonged QT interval, including fatal arrhythmias.

The ACM discussed the available evidence including Australian and international case reports, a literature review, an analysis undertaken by the US Food and Drug Administration and a clinical usage review. Overall, the ACM noted that the case reports provided limited evidence to support this signal and the literature review was inconclusive for this signal due to inconsistent evidence. On balance, the ACM was of the view that the signal is very difficult to interpret, however, at this time, based on the available data, the ACM was unable to definitively state that there is not a signal of harm.

The ACM advised that while the evidence is currently inconsistent, an additional statement regarding the risk of cardiovascular death and requisite precautionary monitoring should be considered for inclusion within the Australian PI. The ACM noted that this proposed addition to the PI should alert but not alarm clinicians and patients.

3.2.3 National Pharmaceutical Regulatory Agency (NPRA) – Malaysia

Azithromycin and cardiovascular death (2025) [29]

In 2025, the NPRA issued a communication on azithromycin and the risk of cardiovascular death.

The communication described the above TGA's review. The Agency noted that they have received 1,254 reports involving 2,190 suspected adverse events related to azithromycin-containing products. While no cases of cardiac death or sudden cardiac death have been reported, there have been 45 reports of cardiac-related adverse events, including ventricular tachycardia, with 7 cases reporting a fatal outcome.

The Agency note that some of these fatalities were attributed to non-cardiovascular causes (eg, sepsis), while the cause of death in most cases remained unknown. In cases where a cardiovascular cause was suspected, the available information was insufficient to establish or exclude a causal association with azithromycin. Contributing factors such as underlying cardiovascular disease, existing comorbidities, concurrent pharmacotherapy, or other confounding variables may have influenced the observed outcomes.

The NPRA has reviewed these reports and continues to closely monitor the safety profile of azithromycin-containing products to assess and respond to any emerging safety concerns.

3.3 New Zealand cases

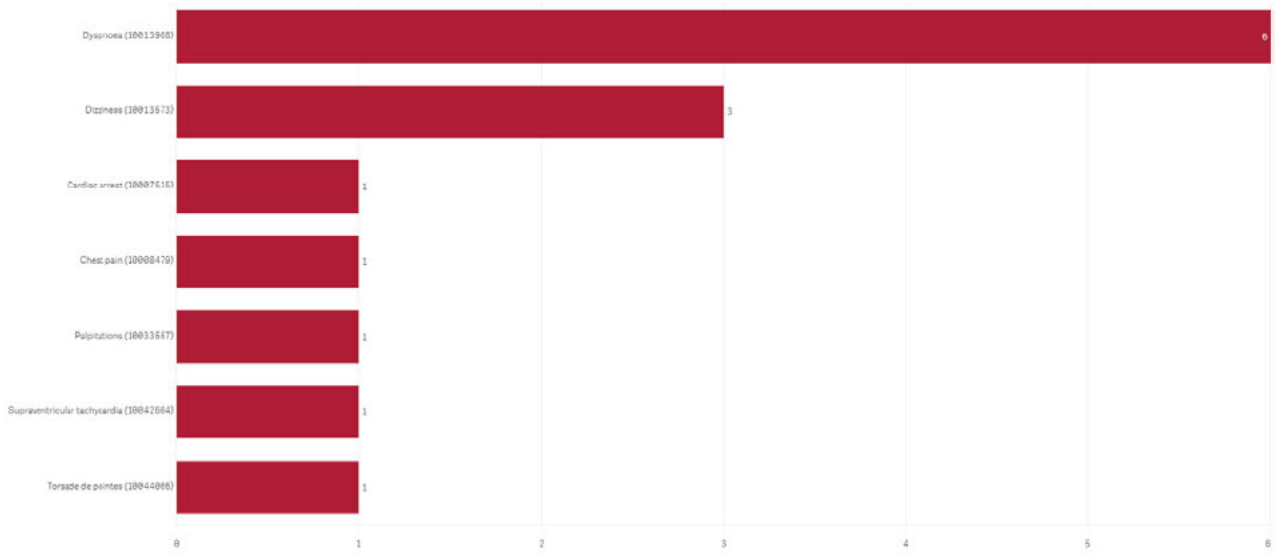
Up to 15 May 2025, a total of 98 cases have been reported to the New Zealand Pharmacovigilance Database containing a MedDRA Preferred Term (PT) under the System Organ Class (SOC) 'cardiac disorder'.

Azithromycin

There were 13 cases where azithromycin was the suspect medicine.

Figure 9 shows the distribution of the MedDRA Preferred Term (PT) under the SOC 'cardiac disorder'. [redacted]

Figure 9: Azithromycin and MedDRA PTs reported under the SOC 'cardiac disorder'

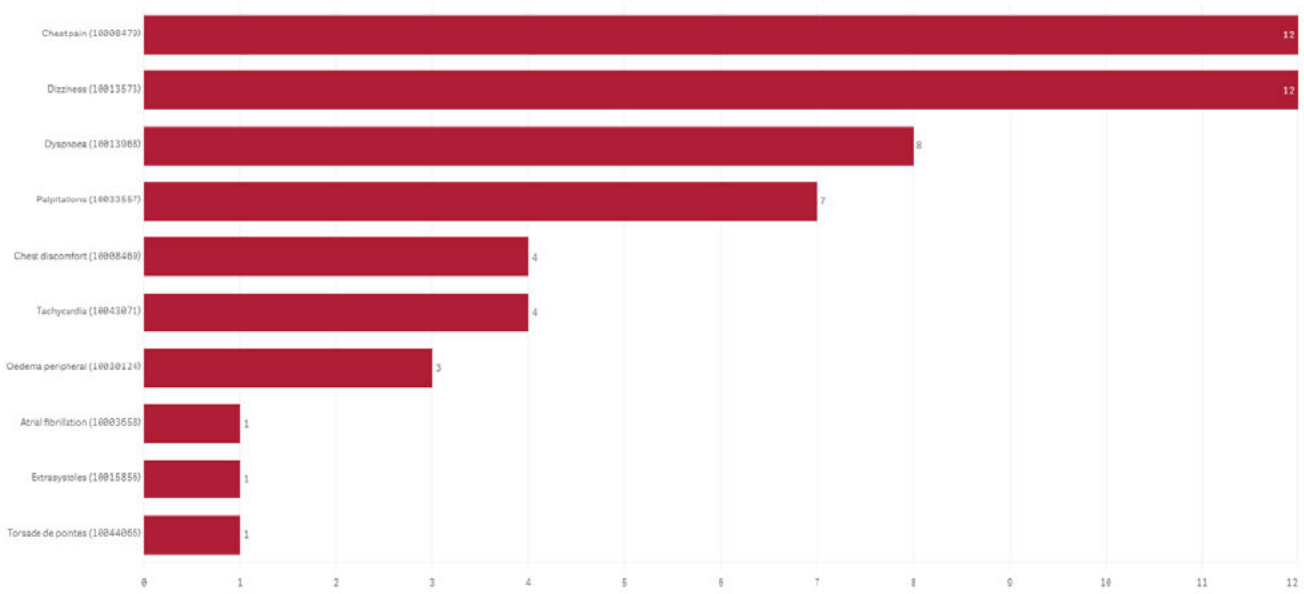


Erythromycin

There were 46 cases where erythromycin was the suspect medicine.

Figure 10 shows the distribution of the MedDRA Preferred Term (PT) under the SOC 'cardiac disorder'. [redacted]

Figure 10: Erythromycin and MedDRA PTs reported under the SOC 'cardiac disorder'

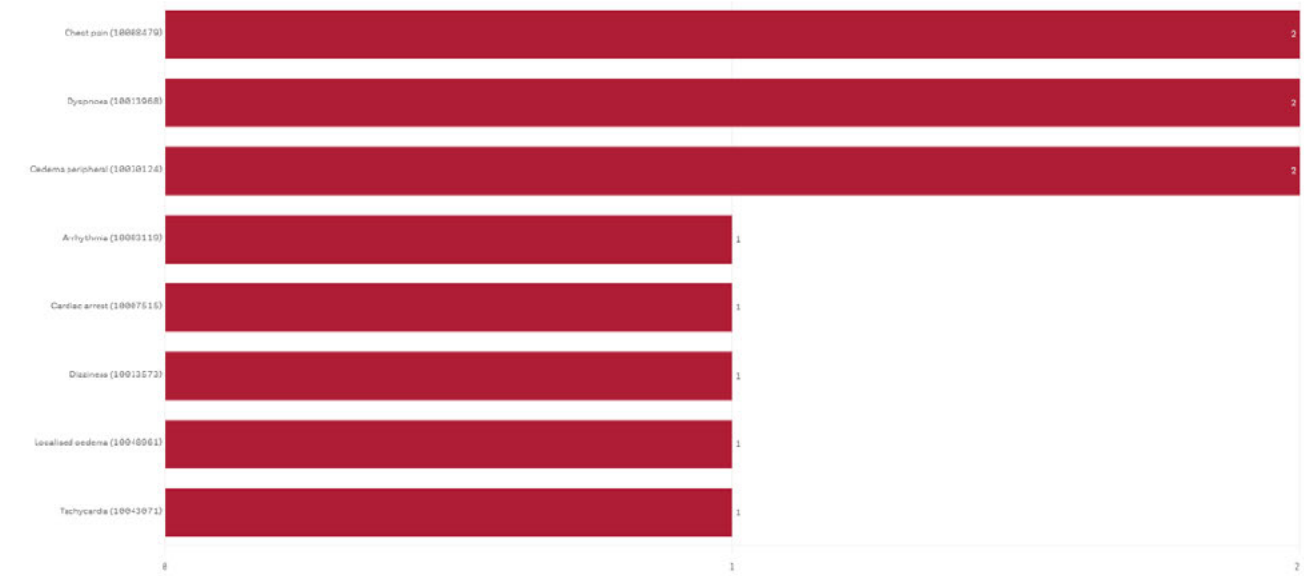


Clarithromycin

There were 9 cases where clarithromycin was the suspect medicine.

Figure 11 shows the distribution of the MedDRA Preferred Term (PT) under the SOC 'cardiac disorder'. [redacted]

Figure 11: Clarithromycin and MedDRA PTs reported under the SOC 'cardiac disorder'

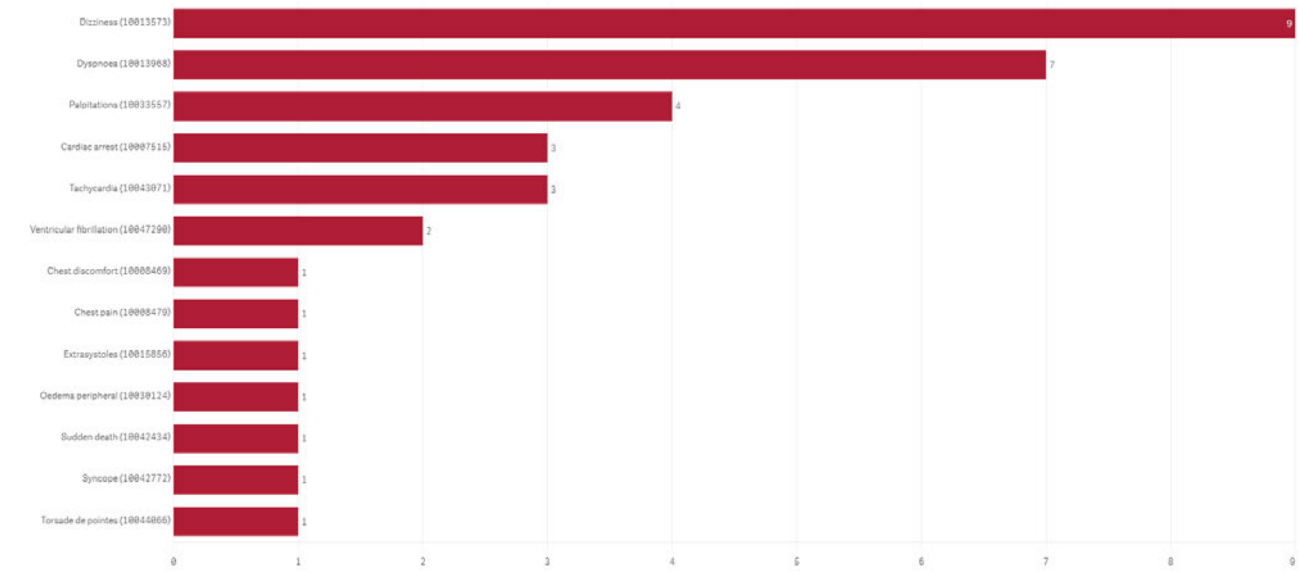


Roxithromycin

There were 30 cases where roxithromycin was the suspect medicine.

Figure 12 shows the distribution of the MedDRA Preferred Term (PT) under the SOC 'cardiac disorder'. [redacted]

Figure 12: Roxithromycin and MedDRA PTs reported under the SOC 'cardiac disorder'



4 DISCUSSION AND CONCLUSIONS

Azithromycin

The most recent retrospective cohort study by Zaroff et al (2020) found an approximately 2-fold increased risk of cardiovascular death within the first 5-days of azithromycin treatment compared to amoxicillin. The risk was also higher in those who had a high baseline cardiovascular risk. The study by Ray et al (2012) had consistent findings. In the Taiwanese population-based study by Chou et al (2014), azithromycin had 2-fold increased risks of ventricular arrhythmia and cardiovascular death compared with amoxicillin + clavulanic acid. Despite the significantly increased risk observed in these studies, the absolute risk was very small, especially in patients without underlying cardiovascular disease.

In contrast, Svanstrom et al (2013) did not find an association between cardiovascular death with azithromycin compared to use of penicillin V, although this study used the Danish database which had a relatively younger mean age compared to the above studies. Mortensen et al (2015) did not find an association with azithromycin and cardiovascular death, but instead azithromycin was associated with decreased mortality. Sutton et al (2017) showed that mortality rates between azithromycin users versus users of other study antibiotics were not significantly different and therefore the findings by Ray et al (2012) may not be applicable to the general population who are not at risk.

Finally, a meta-analysis from Bin Abdulhak et al (2015) included five observational studies with eight results from determining the primary outcome risk of death (cardiovascular and/or non-cardiovascular causes). Azithromycin use for 1-10 days was not associated with an increased risk of cardiovascular death. However, current use (within 5 days) of azithromycin in an older population was associated with an increased risk of death (all cause).

Azithromycin is known to prolong the QT interval, which can lead to TdP. Episodes of TdP can recur in rapid succession, potentially degenerating to ventricular fibrillation and sudden cardiac death.

The increased risk of cardiovascular death may be explained by the above proarrhythmic effect, however other unknown mechanisms may also be at play.

To illustrate this, Zaroff et al (2020) observed a proportion of cardiovascular deaths to be sudden deaths and thus suggestive of arrhythmia. There were more deaths related to other cardiac conditions. There is not a clear mechanism to explain how azithromycin would directly cause those deaths [30].

The US and Australian product information has specific warning on the short term (5 days) risk of cardiovascular death. However, differences between the Australian and US product information are noted:

- The US labelling says that the risk does not appear to be limited to those with pre-existing cardiovascular disease.
- The Australian product information advises to consider performing a screening ECG in patients whose medical history and/or on-going medical treatments place them at high risk for a prolonged QTc.

The New Zealand data sheet does not include a warning on an increased risk of cardiovascular death.

Other macrolides

Clarithromycin

There are conflicting findings from individual observational studies on the use of clarithromycin and the risk of cardiovascular death. The Danish based registry study by Inghammar et al (2017) and the Taiwanese-based study by Chou et al (2014) did not find an association from the use of clarithromycin and cardiovascular death as compared with penicillin V and amoxicillin respectively. Whereas Svanstrom et al (2014) and Wong et al (2016) observed an increased risk of cardiac death associated with current use of clarithromycin, compared to penicillin V and amoxicillin respectively.

Results from meta-analyses were also conflicting.

The current New Zealand clarithromycin data sheet has a warning that appropriately reflects the conflicting literature findings on the risk of cardiovascular death.

Erythromycin

There were too few studies on erythromycin to be included in the meta-analyses by Wu et al (2023) and Cheng et al (2015).

One observational study found that the risk of sudden death from cardiac causes was twice as high among current users of erythromycin compared to other antibiotics, greater among those who were concomitantly using a CYP 3A4 inhibitor (Ray et al 2004).

The current New Zealand ERA (erythromycin stearate) data sheet has a warning that appropriately reflects the conflicting literature findings on the risk of cardiovascular death. However, the E-mycin (erythromycin ethyl succinate) data sheet does not have the same information.

Roxithromycin

This macrolide is not widely used internationally. However, in New Zealand, roxithromycin is the most frequently dispensed macrolide. Individual observational studies and meta-analyses did not support an association between use of roxithromycin and cardiovascular death.

The New Zealand roxithromycin data sheet does not include a warning on cardiovascular death.

Conclusions

Overall, observational studies and meta-analyses showed inconsistent findings on the use of azithromycin and clarithromycin and the risk of cardiovascular death. There were not many individual studies with erythromycin in the meta-analysis so it was therefore hard to draw any conclusions. In contrast the literature on roxithromycin does not appear to support an increased risk of cardiovascular death.

The inconsistent findings for some macrolides may be a result of the limitations of cohort studies, such as confounding by indication (eg, patients prescribed macrolides may be sicker and have higher cardiovascular risk than patients taking other types of antibiotics or no antibiotics; therefore, the increased risk observed in

some studies may be related to the acute infection itself), different source populations (by age, ethnicity and country) and unmeasured confounders. In many studies there were incomplete data provided, such as lack of reporting of indication and confounders that were not considered but associated with the outcome (such as BMI and the smoking status of the patient).

Internationally, the main attention has been on azithromycin and clarithromycin and risk of cardiovascular death, but not on other macrolides.

Reports in the New Zealand pharmacovigilance database does not suggest an association between macrolides and an increased risk of cardiovascular death.

5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence in the scientific literature for an association between
  - azithromycin
  - erythromycin
  - clarithromycin
  - roxithromycin

  and an increased risk of cardiovascular death.
- Whether a warning statement (section 4.4) is required in all macrolide data sheets, or only certain macrolides?
- Whether the term cardiovascular death should be included as an undesirable effect (section 4.8) in all macrolide data sheets or only certain macrolides?
- Whether further communication is required, other than in MARC's remarks?

6 REFERENCES

1. United States Food and Drug Administration. 2021. *NDA 050693/S-034 and 050730/S-043* 22 November 2021. URL: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/050693Orig1s034;050730Orig1s043ltr.pdf (accessed 26 May 2025).
2. New Zealand Formulary. 2025. *NZF v155 5.1.5 Macrolides* 1 May 2024. URL: https://nzf.org.nz/nzf_3146?searchterm=macrolides (accessed 22 May 2025).
3. Patel PH and Hashmi MF. 2023. *Macrolides in StatPearls* 16 May 2023. URL: https://www.ncbi.nlm.nih.gov/books/NBK551495/ (accessed 22 May 2025).
4. Cheng YJ, Nie XY, Chen XM, et al. 2015. The Role of Macrolide Antibiotics in Increasing Cardiovascular Risk. *J Am Coll Cardiol* 66(20): 2173-2184. 10.1016/j.jacc.2015.09.029 (accessed 22 May 2025).
5. Berul CI. 2022. *Acquired long QT syndrome: Definitions, pathophysiology, and causes. In UpToDate.* 21 September 2022. URL: https://www.uptodate.com/contents/acquired-long-qt-syndrome-definitions-pathophysiology-and-causes?sectionName=DEFINITIONS&topicRef=116011&anchor=H1125272528&source=see_link#H1125272528 (accessed 23 August 2023).
6. Yow AG, Rajasurya V, Ahmen I, et al. 2024. *Sudden Cardiac Death in StatPearls* 16 May 2024. URL: https://www.ncbi.nlm.nih.gov/books/NBK507854/ (accessed 22 May 2025).
7. Gharios C, Leblebjian M, Mora S, et al. 2021. The association of cardiovascular mortality with a first-degree family member history of different cardiovascular diseases. *J Geriatr Cardiol* 18(10): 816-824. 10.11909/j.issn.1671-5411.2021.10.001 (accessed 22 May 2025).
8. Heart Foundation New Zealand. *General heart statistics in New Zealand* URL: https://www.heartfoundation.org.nz/statistics (accessed 22 May 2025).

9. Zaroff JG, Cheetham TC, Palmetto N, et al. 2020. Association of Azithromycin Use With Cardiovascular Mortality. *JAMA Netw Open* 3(6): e208199. 10.1001/jamanetworkopen.2020.8199 (accessed 5 May 2025).
10. Ray WA, Murray KT, Hall K, et al. 2012. Azithromycin and the Risk of Cardiovascular Death. *New England Journal of Medicine* 366(20): 1881-1890. doi:10.1056/NEJMoa1003833 (accessed 5 May 2025).
11. Assimon MM, Pun PH, Wang L, et al. 2022. Azithromycin use increases the risk of sudden cardiac death in patients with hemodialysis-dependent kidney failure. *Kidney Int* 102(4): 894-903. 10.1016/j.kint.2022.05.024 (accessed 5 May 2025).
12. Rao GA, Mann JR, Shoaibi A, et al. 2014. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med* 12(2): 121-7. 10.1370/afm.1601 (accessed 5 May 2025).
13. Svanström H, Pasternak B and Hviid A. 2013. Use of azithromycin and death from cardiovascular causes. *N Engl J Med* 368(18): 1704-12. 10.1056/NEJMoa1300799 (accessed 5 May 2025).
14. Mortensen EM, Halm EA, Pugh MJ, et al. 2014. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *Jama* 311(21): 2199-208. 10.1001/jama.2014.4304 (accessed 5 May 2025).
15. Sutton SS, Hyche S, Magagnoli J, et al. 2017. Appraisal of the cardiovascular risks of azithromycin: an observational analysis. *J Comp Eff Res* 6(6): 509-517. 10.2217/cer-2016-0080 (accessed 5 May 2025).
16. Chou HW, Wang JL, Chang CH, et al. 2015. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis* 60(4): 566-77. 10.1093/cid/ciu914 (accessed 5 May 2025).
17. DerSarkissian M, Young-Xu Y, Duh MS, et al. 2022. The acute effects of azithromycin use on cardiovascular mortality as compared with amoxicillin-clavulanate in US Veterans. *Pharmacoepidemiol Drug Saf* 31(8): 840-850. 10.1002/pds.5451 (accessed 5 May 2025).
18. Bin Abdulhak AA, Khan AR, Garbati MA, et al. 2015. Azithromycin and Risk of Cardiovascular Death: A Meta-Analytic Review of Observational Studies. *Am J Ther* 22(5): e122-9. 10.1097/mjt.0000000000000138 (accessed 5 May 2025).
19. Inghammar M, Nibell O, Pasternak B, et al. 2018. Long-Term Risk of Cardiovascular Death With Use of Clarithromycin and Roxithromycin: A Nationwide Cohort Study. *Am J Epidemiol* 187(4): 777-785. 10.1093/aje/kwx359 (accessed 22 May 2025).
20. Svanström H, Pasternak B and Hviid A. 2014. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. *BMJ : British Medical Journal* 349(g4930. 10.1136/bmj.g4930 (accessed 22 May 2025).
21. Wong AYS, Root A, Douglas IJ, et al. 2016. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ* 352(h6926. 10.1136/bmj.h6926 (accessed 22 May 2025).
22. You CH, Lin CK, Chen PH, et al. 2019. Clarithromycin use and the risk of mortality and cardiovascular events: A systematic review and meta-analysis. *PLoS One* 14(12): e0226637. 10.1371/journal.pone.0226637 (accessed 22 May 2025).
23. Ray WA, Murray KT, Meredith S, et al. 2004. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 351(11): 1089-96. 10.1056/NEJMoa040582 (accessed 22 May 2025).
24. Wu Y, Bi WT, Qu LP, et al. 2023. Administration of macrolide antibiotics increases cardiovascular risk. *Front Cardiovasc Med* 10(1117254. 10.3389/fcvm.2023.1117254 (accessed 22 May 2025).
25. Li X, Wang M, Liu G, et al. 2016. Association of macrolides with overall mortality and cardiac death among patients with various infections: A meta-analysis. *Eur J Intern Med* 28(32-7. 10.1016/j.ejim.2015.09.009 (accessed 22 May 2025).
26. United States Food and Drug Administration. 2018. *FDA Drug Safety Communication: FDA review finds additional data supports the potential for increased long-term risks with antibiotic clarithromycin (Biaxin) in patients with heart disease* 22 Feburary 2018. URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long (accessed 22 May 2025).

27. Therapeutic Goods Administration. 2024. *Azithromycin and rare risk of cardiovascular death* 1 August 2024. URL: https://www.tga.gov.au/news/safety-updates/azithromycin-and-rare-risk-cardiovascular-death (accessed 22 May 2025).
28. Therapeutic Goods Administration. 2023. *ACM meeting statement, Meeting 42, 30 November and 1 December 2023* 29 December 2023. URL: https://www.tga.gov.au/resources/publication/meeting-statements/acm-meeting-statement-meeting-42-30-november-and-1-december-2023 (accessed 5 May 2025).
29. National Pharmaceutical Regulatory Agency – Malaysia. 2025. *Azithromycin: Rare Risk of Cardiovascular Death* 24 April 2025. URL: https://npra.gov.my/index.php/en/component/content/article/465-english/safety-alerts-main/safety-alerts-2025/1527709-azithromycin-rare-risk-of-cardiovascular-death.html?Itemid=1391 (accessed 5 May 2025).
30. Cox CE. 2020. *Azithromycin Again Linked to Higher CV Mortality Risk in TCTMD* 23 June 2020. URL: https://www.tctmd.com/news/azithromycin-again-linked-higher-cv-mortality-risk (accessed 22 May 2025).