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## Cardiac risks associated with antibiotics: azithromycin and levofloxacin

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### Abstract

**Introduction**—Azithromycin and levofloxacin have been shown to be efficacious in treating infections. The adverse drug events associated with azithromycin and levofloxacin were considered rare. However, the US FDA released warnings regarding the possible risk of QT prolongation with azithromycin and levofloxacin.

**Areas covered**—Case reports/case series, observational studies and clinical trials assessing cardiovascular risks associated with azithromycin and levofloxacin were critically reviewed, including 15 case reports/series, 5 observational studies and 5 clinical trials that investigated the cardiac risks associated azithromycin and levofloxacin.

**Expert opinion**—Results are discordant. Two retrospective studies utilizing large databases demonstrated an increased risk of cardiovascular death with azithromycin, when azithromycin was compared with amoxicillin. Two other retrospective studies found no difference in cardiovascular death associated with azithromycin and other antibiotics. For levofloxacin, the increased risk of cardiovascular death was only found in one retrospective study. Therefore, the risks and benefits of antibacterial therapies should be considered when making prescription decisions. This study should not preclude clinicians from avoiding azithromycin and levofloxacin. If a patient has an

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#### Declaration of interest

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indication to receive an antibiotic and if azithromycin or levofloxacin is needed, it may be used, but the potential risks must be understood.

### Keywords

adverse drug reactions; antibiotics; azithromycin; cardiac death; cardiovascular risks; drug safety; infections; levofloxacin; review

## 1. Introduction

Azithromycin and levofloxacin are the most frequently used antibiotics in the US. Azithromycin is a semisynthetic macrolide antibiotic, whereas levofloxacin is a fluoroquinolones antibiotic. Since its release in early 1990s, azithromycin has become the most commonly prescribed macrolide antibiotics in the US. In 2010, 53.6 million prescriptions were filled for azithromycin [1,2]. Additionally, levofloxacin was approved by the US FDA in late 1990s, and the number of dispensed prescriptions for oral levofloxacin in 2010 was 9.3 million [3]. Although azithromycin and levofloxacin belong to different classes of antibiotics, both drugs are used alone or in combination with other antibiotics to treat common bacterial infections, including respiratory infections, sexually transmitted diseases, urinary tract infections and uncomplicated skin and soft tissue infections [3–5].

The side effects associated with azithromycin and levofloxacin are well recognized. However, studies by Ray *et al.* led to additional concerns for potential adverse cardiac risks [6,7]. The labeling of levofloxacin included prolongation of the QT interval warning based on case reports/series of QT interval-related events in the FDA's MedWatch system [8]. In 2012, the FDA released a statement to warn healthcare professionals regarding the azithromycin-induced potential QT prolongation and fatal torsades de pointes (TdP) [9]. The warning included a statement that the risks of cardiovascular death associated with azithromycin were similar to levofloxacin. More recently, however, Svanström and Rao suggested that azithromycin was not associated with increased cardiac risks [7,10]. The objectives of this article are to critically review recently published articles accessing adverse cardiac effects of azithromycin and levofloxacin, explain possible mechanisms of these effects and provide expert opinions and suggestions.

## 2. Electrophysiological mechanisms

The QT interval is the time measure between the start of the Q wave and the end of the T wave in the heart's electrical cycle [11]. The QT interval represents depolarization and repolarization of the ventricles. Based on the estimates from population-based studies, normal values for the QT interval is < 430 ms for men and < 450 ms for women, respectively [12]. If the QT interval is > 500 ms or the prolongation of QT interval is > 60 ms, it is commonly considered a sign of increased cardiac risks [13].

Prolongation of QT interval does not solely have adverse effects on cardiac function, but it can cause early after depolarizations (EADs). If EAD reaches the threshold electrical potential, it may induce polymorphic ventricular tachycardia, which is also known as TdP [14]. TdP may cause dizziness, palpitations, seizures, ventricular fibrillations, cardiac arrests

and sudden deaths. However, the predication of TdP cannot be solely based on the presence of prolonged QT interval, because the QT interval is not perfectly correlated with TdP [15].

Prolonged QT interval are reported to be associated with several clinical risk factors, such as advanced age [16], female sex [17], hepatic and renal dysfunction, electrolyte disturbance (hypokalemia, hypomagnesemia and hypocalcemia), bradycardia and concomitant use of diuretics or other QT-prolonging medications [14,18]. The drugs associated with QT prolongation include antiarrhythmic drugs (quinidine, procainamide, disopyramide), antipsychotics (ziprasidone, risperidone, zimelidine, citalopram), antidepressants (amitriptyline, desipramine, imipramine, maprotiline, doxepin, fluoxetine), quinolone antibiotics (levofloxacin, moxifloxacin), macrolide antibiotics (erythromycin, clarithromycin) and others [13,18].

The exact mechanism by which macrolides and fluoroquinolones prolong the QT interval is through a blockade of the rapid component, IKr, of the delayed rectifier potassium current IK, which is encoded by the human ether-a-go-go related gene 1(hERG1). The IKr regulates outward flow of potassium ions from ventricular myocytes to the extracellular fluid and stimulates ventricular repolarization. Inhabitation of IhERG can block the outward flow of potassium, which leads to intracellular accumulation of potassium and ventricular repolarization and results in QT prolongation and TdP [19].

Drug–drug interaction may also be an explanation for prolonged QT interval. When azithromycins are used with other QT-prolonging drugs, they may inhibit CYP enzymes and reduce the metabolism of other drugs by forming an inactive CYP complex. QT-prolonging drugs, such as antihistamine and antiarrhythmic agents, may be potentiated, leading to QT prolongation [20].

### 3. Cardiovascular effects

To examine the cardiac risks associated with azithromycin and levofloxacin, we conducted a literature search focusing on azithromycin but also include levofloxacin using MEDLINE from January 1980 to August 2014 with terms including ‘azithromycin’, ‘levofloxacin’, ‘cardiovascular death’, ‘cardiovascular risk’, ‘QT prolongation’, ‘QT’, ‘torsades de pointes’ and ‘arrhythmia’. After excluding articles that were unrelated to the topic, we found 5 clinical trials, 5 observational studies and 15 case reports/case series of azithromycin and levofloxacin. The results of observational studies were summarized in Table 1. Clinical trials [21–24] were not included here for review because they examined the effect of azithromycin in the secondary prevention of coronary events, which is out of the scope of this review.

#### 3.1 Azithromycin

In the first case of QT prolongation that developed after azithromycin treatment, Granowitz *et al.* reported that the patient also received disopyramide in conjunction with azithromycin [25]. QT prolongation can also occur in patients with preexisting congenital long QT syndrome [26] or congestive heart failure [27–30]. Huang *et al.* documented that QT interval was prolonged after the initiation of azithromycin treatment but returned to normal after

discontinuation of the therapy [31]. QT prolongation was also observed in patients with hypokalemia, HIV, using methadone, moxifloxacin or ciprofloxacin [32–35].

To examine the effect of QT prolongation associated with azithromycin in healthy people, Strle and Maraspin conducted a prospective observational study that included 31 female and 16 male participants aged 19 to 77 years [36]. The participants received azithromycin 500 mg twice daily on day 1 followed by 500 mg/day for 4 days, without using other medications. Electrocardiography (ECG) was monitored before and after the initiation of azithromycin. The azithromycin was associated with mild prolongation of QT interval on treatment for 7 days (412.5 ms) and 14 days (419 ms), compared to the previously recorded QT interval (406 ms). However, the proportion of participants with QT intervals greater than the upper normal value of 440 ms was reported same before and after the azithromycin treatment.

A randomized, placebo-controlled clinical trial was conducted in 116 healthy subjects who received either chloroquine 1000 mg alone or chloroquine with the coadministration of azithromycin (500, 1000 or 1500 mg) [37]. Compared to chloroquine alone, chloroquine in combination with azithromycin was associated with a dose-dependent QT prolongation. The maximal mean prolongation with the coadministration of azithromycin 500, 1000 and 1500 mg was 5 ms (95% upper CI: 10 ms), 7 ms (95% upper CI: 12 ms) and 9 ms (95% upper CI: 14 ms), respectively, which could be considered as potentially clinically significant, according to the FDA definitions.

Concerns about cardiac risks from azithromycin and levofloxacin largely emerged after the *New England Journal of Medicine* published a retrospective study comparing azithromycin, amoxicillin, ciprofloxacin, levofloxacin and no antibiotic among the Tennessee Medicaid enrollees between 1992 and 2006 [6]. This study included patients aged between 30 and 74 years and had no diagnosis of drug abuse and life-threatening noncardiovascular diseases. The study end points were cardiovascular death (including sudden cardiac death and other cardiovascular events) and all-cause death. Compared to those receiving no antibiotics, patients taking a 5-day course of azithromycin had a significant increased risk of cardiovascular death (hazard ratio [HR]: 2.88, 95% CI: 1.79 – 4.63) and all-cause death (HR: 1.85, 95% CI: 1.25 – 2.75), whereas patients taking amoxicillin had no increase in the risk of death during this period. When compared to amoxicillin, azithromycin was associated with a significant increased risk of cardiovascular death (HR: 2.49, 95% CI: 1.38 – 4.50) and death from any cause (HR: 2.02, 95% CI: 1.24 – 3.30). However, there is no significant differences in the risk of cardiovascular death between azithromycin and levofloxacin (HR: 1.27, 95% CI: 0.66 – 2.47).

The second retrospective cohort study compared the risk of cardiovascular death in general population aged 18 – 64 years receiving azithromycin with those patients receiving no antibiotics and penicillin V in Denmark between 1997 and 2010 [10]. The study sample was limited to young and middle-aged adults to adjust for the potential confounding variables related to aging, such as cardiovascular risk factors. The study cohort included patients who took oral azithromycin or penicillin V and had not been hospitalized. The primary outcome of interest was cardiovascular death and the secondary outcome was noncardiovascular

death. The deaths were categorized based on current use (1 – 5 days), recent use (6 – 10 days) and past use (10 – 35 days) of azithromycin. Compared to no use of antibiotic therapy, current use of azithromycin was associated with a significantly increased risk of cardiovascular death (rate ratio [RR]: 2.85, 95% CI: 1.13 – 7.24); however, significant results were not observed in recent or past use of azithromycin (RR: 1.44, 95% CI: 0.46 – 4.54; RR: 0.69, 95% CI: 0.41 – 1.17, respectively). After adjusting for propensity scores, for any users of azithromycin compared to penicillin V, no association was observed with the risk of cardiovascular death (RR: 0.93, 95% CI: 0.56 – 1.55; RR: 0.75, 95% CI: 0.34 – 1.62; and RR: 0.92, 95% CI: 0.60 – 1.42, respectively).

Rao *et al.* conducted a retrospective study among the US veterans who had an outpatient pharmacy claim of either amoxicillin, azithromycin or levofloxacin at the Department of Veterans Affairs between September 1999 and April 2012 [7]. Patients were included in the cohort if they were between 30 and 74 years, without life-threatening noncardiovascular illness and drug abuse. The primary end point of the study was all-cause mortality; and the secondary end point was serious cardiac arrhythmia, defined as any utilization for cardiac arrhythmia encountered in inpatient or emergency department identified by using International Classification of Disease, Ninth Revision, Clinical Modification codes. Compared with patients receiving amoxicillin, patients receiving azithromycin had significantly increased risk of death (HR: 1.48, 95% CI: 1.05 – 2.09) and serious arrhythmia (HR: 1.77, 95% CI: 1.20 – 2.62) on treatment days 1 to 5; risks of death and serious arrhythmia were not statistically different during treatment days 6 to 10.

The most recently published retrospective cohort study was performed using national Department of Veterans Affairs' administrative data [38]. The risk of cardiovascular death was compared in patients aged  $\geq 65$  years and hospitalized with pneumonia to those receiving guideline-concordant antibiotic therapy from fiscal years 2002 to 2012. Compared those taking other antibiotics, 90-day mortality was significantly lower in patients who used azithromycin (17.4 vs 22.3%; odds ratio [OR]: 0.73, 95% CI: 0.70 – 0.76). However, increased risks of myocardial infarction was observed in patients receiving azithromycin, compared to other antibiotics (5.1 vs 4.0%; OR: 1.17, 95% CI: 1.08 – 1.25), but it did not reach statistical significance in cardiac events (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).

### 3.2 Levofloxacin

Paltoo *et al.* reported the first case of polymorphic ventricular tachycardia in response to the use of levofloxacin in patients with no risk factors [39]. Patel *et al.* reported that polymorphic ventricular tachycardia occurred in a 91-year-old woman with flu-like symptoms after using levofloxacin [40]. QT prolongation and TdP were also observed in patients using levofloxacin [41,42].

Tsikouris *et al.* conducted an open-label crossover study including 13 healthy subjects. Each participant received the following in random order: ciprofloxacin 500 mg twice daily, levofloxacin 500 mg/day and moxifloxacin 400 mg/day. Levofloxacin had no significant

effect on QTc interval, whereas moxifloxacin was associated with QTc prolongation of 6 ms relative to baseline (408 ms,  $p = 0.022$ ) [43].

In the clinical trial by Noel *et al.*, change in QT interval was compared between levofloxacin and placebo in healthy volunteers. For those receiving levofloxacin, compared to placebo, the change in QT interval ranged from 3.53 to 4.88 ms relative to the baseline ( $p < 0.05$ ) [44].

Makaryus *et al.* evaluated the effect of levofloxacin on the QT interval in 38 adults with community-acquired pneumonia or urinary tract infections. Twelve-lead ECGs were monitored at baseline and at least 48 h after the administration of the first dose of levofloxacin. A statistically significant increase in the longest QTc intervals relative to baseline was observed in patients receiving levofloxacin. However, levofloxacin did not significantly prolong the mean QTc interval over the baseline [45].

Morganroth *et al.* conducted a randomized, double-blind trial at 47 hospitals in the US. A total of 387 elderly patients with community-acquired pneumonia were recruited in the study. The primary end point of this study was a composite of ventricular arrhythmia events based on Holter monitoring. Sixteen (8.3%) primary composite cardiac events were found in patients receiving moxifloxacin, and 10 events (5.1%) were found in levofloxacin-treated patients ( $p = 0.29$ ); there were no significant differences in the cardiac rhythm safety between moxifloxacin and levofloxacin [46].

In Ray *et al.*'s study [6], compared with patients treated with amoxicillin, patients using levofloxacin were associated with nonsignificant increase in the risk of cardiovascular deaths (HR: 1.50, 95% CI: 0.82 – 2.72) and all-cause deaths (HR: 1.15, 95% CI: 0.75 – 1.77).

Rao *et al.* suggested that levofloxacin, when compared to amoxicillin, was associated with a greater risk of death (HR: 2.49, 95% CI: 1.7 – 3.64) and serious cardiac arrhythmia (HR: 2.43, 95% CI: 1.56 – 3.79) for days 1 to 5, and it would remain significantly different on days 6 to 10 for deaths (HR: 1.95, 95% CI: 1.32 – 2.88) and arrhythmia (HR: 1.75, 95% CI: 1.09 – 2.82) [7].

#### 4. Discussion

Based on the studies reviewed, QT prolongation could not be associated with the use of azithromycin and levofloxacin in the clinical studies reviewed [36,43–46]. There are arguments for an increased risk of cardiac adverse events and death observed in case reports/series and observational studies. However, the increased risks may also be explained by other factors, such as coexisting conditions, concomitant medication use or the limitation of study designs.

First, the majority of cases reviewed above involved patients with multiple comorbidities such as hypertension, heart failure, chronic obstructive pulmonary disease (COPD) diabetes and risk factors associated with QT prolongation. There is evidence of azithromycin-induced QT prolongation and TdP observed in patients with hypokalemia, HIV, previous history of

cardiac abnormalities and in those patients concomitantly taking other QT-prolonging drugs, such as trazodone and methadone. Hence, it is difficult to isolate azithromycin as a sole factor resulting in QT prolongation or TdP in the case reports/series reviewed in Section 3.

Second, the recently published observational studies reported inconsistent results in the cardiac risks associated with azithromycin and levofloxacin [6,7,10,38]. Although these studies are generally well designed, there are potential issues that may lead to these conflicting results due to the nature of observational studies. In the cohort studies by Rao *et al.* [7] and Ray *et al.* [6], subjects receiving azithromycin or levofloxacin may be more likely to have serious infections than those using amoxicillin, thus leading to a higher likelihood of death. In fact, these increased mortalities might be explained by acute infection alone [47]. Moreover, due to the lack of randomization, the imbalances between azithromycin or levofloxacin and comparator group may result in contradicted conclusions drawn in the cohort studies. For instance, Ray *et al.* included more women in the azithromycin group. Women tend to have longer QT intervals and higher risk of TdP than men largely because of the effects of sex hormones on myocardial tissue [17,48–54]. It is reported that Ray *et al.* might overestimate the risk of azithromycin-related cardiac deaths by ~ 30%. This overestimation largely contributed to the significant association observed between azithromycin use and cardiac deaths [55].

Third, it is also possible that azithromycin and levofloxacin affect adversely on the cardiovascular profile. This can only be observed in patients with risk factors of QT prolongation, such as the use of QT-prolonging medications.

Interestingly, in the clinical trials, azithromycin and levofloxacin did not demonstrate significant QT/QTc prolongation in healthy people [31,43,44]. Although prolonged QT interval is not a strong indicator for predicting the TdP and adverse cardiac events, the data from the clinical trials are still valuable in understanding the cardiac safety of azithromycin and levofloxacin.

Data obtained from case reports/series, observational studies and clinical trials have led to some understanding of the potential association between cardiac risk with azithromycin and levofloxacin. However, the current studies evaluating the cardiac safety profile of azithromycin and levofloxacin are imperfect for drawing a firm conclusion in both individual and population levels. Considering the wide use of azithromycin and levofloxacin in infectious diseases, there is a greater need for further examination of their cardiovascular safeties, particularly for patients with common infections, such as community-acquired pneumonia.

## 5. Conclusion

In summary, although cardiovascular safety of azithromycin and levofloxacin is still inconclusive, when an indication is presented, clinicians should not be reluctant to prescribe them. However, the decision to initiate azithromycin or levofloxacin treatment should be based on a careful evaluation of the preexisting comorbidities, risk factors of QT prolongation and concomitant medication use. Moreover, ECG should be monitored periodically for patients with an especially high risk of arrhythmia. Risk factors for QT

prolongation include hypomagnesemia, hypokalemia and concomitant administration of QT-prolonging drugs. However, there is no 'safe' QT prolongation, even though the lesser the potassium blockade, the rarer is the risk.

## 6. Expert opinion

Azithromycin is frequently prescribed because of indications, antimicrobial activity, favorable drug interaction profile and convenience of dosing, compared to erythromycin and clarithromycin [56]. Compared with other macrolides, azithromycin was considered as having minimal cardiovascular toxicity, whereas other macrolide antibiotics – erythromycin and clarithromycin – are associated with increased risk of adverse cardiovascular events, such as cardiac arrhythmias, TdP and cardiovascular death [57]. Azithromycin may be least likely to cause QT prolongation and cardiac arrhythmias in the macrolides. The rank order of causing QT prolongation in humans was erythromycin > clarithromycin > roxithromycin > azithromycin [8]. In addition to the different effects on QT interval, with decreased potassium concentrations, azithromycin did not lead to EADs and related TdP, whereas erythromycin and clarithromycin did [58]. Shaffer *et al.* searched the adverse event reporting system of the FDA [57]. A total of 156 cases of TdP related to the use of a macrolide were found from 1987 to 2000, with one-half (78) of them with no concomitant administration of drugs that prolonged the QT interval. TdP in response to azithromycin was rarely reported; only 12 cases (15% of all reports) of TdP were reported in the use of azithromycin, whereas erythromycin and clarithromycin use were documented in 53 and 36% of all reports, respectively; azithromycin demonstrated more favorable cardiovascular safety profiles than other macrolides, based on the existing evidence. Although other macrolides may increase the QTc more than azithromycin, azithromycin still led to cardiovascular risks in selected studies.

Levofloxacin is most frequently used in the class of fluoroquinolone antibiotics. *In vitro* studies showed that levofloxacin were less likely to induce TdP compared to other fluoroquinolone antibiotics. In the animal studies, levofloxacin demonstrated less prominent effect on the potential duration in isolated guinea pig myocardia than those of moxifloxacin, sparfloxacin, grepafloxacin and gatifloxacin [59]. In the FDA's adverse event reporting system from 2004 to 2008, levofloxacin was more frequently reported to induce TdP among antibacterial agents. A total of 230 cases of TdP were found to be related to the administration of antibacterial agents, whereas 55 cases were associated with the use of levofloxacin [60].

Although the link between azithromycin or levofloxacin use and cardiovascular risk is still inconclusive, clinicians should be aware of patient-specific conditions before prescribing azithromycin or levofloxacin. The major factors related to the incidence of QT prolongation and TdP are the preexisting risk factors of QT prolongation, the cardiac adverse effects induced by azithromycin or levofloxacin alone, and their coadministration with other drugs prolong QT interval [57].

In general, clinicians should be aware that azithromycin and levofloxacin are relatively safe for patients without complications or additional risk factors of QT prolongation, and



decision regarding the initiation of medication therapy should be made on a case-by-case basis. Based on case reports/series, most of the patients experiencing adverse cardiac consequences in response to azithromycin and levofloxacin had at least one risk factor for developing QT prolongation. Mosholder *et al.* concluded that the likelihood of azithromycin-associated cardiovascular death would be increased by > 24-fold if the patient had a risk factor for QT prolongation [61]. In addition to the comorbidities of concern, caution should be warranted for patients with concomitant use of medications that can prolong QT interval, such as antiarrhythmics [62–64]. When prescribing for patients with more risk factors, it would be ideal to perform additional monitoring. For patients with a high risk of cardiac adverse event, alternative drugs should be considered.

To prevent the incidence of cardiac adverse effects, several steps should be considered.

First, risk factors and concomitant medications should be screened and evaluated before starting treatment [65]. Albert and Schuller screened patients with COPD by performing an ECG before azithromycin use, documenting the history of heart failure, episodes of hypokalemia, a family history of prolonged QT or use of other medications that is potential to prolong the QT interval, and conducted an ECG before starting the medication therapy [55,66]. This approach was considered as cost-effective by Berg *et al.*, because lower all-cause mortality was observed in azithromycin than placebo [67].

Second, in outpatient setting, patients should be educated on reporting symptoms of dizziness, palpitations or syncope. It seems prudent to perform a baseline ECG and monitor it during the treatment, although the applicability might be another problem.

Third, if the QT interval gets over 500 ms, patients should be dutifully monitored until the ECG gets back to normal. A QTc increase > 480 or 60 ms from baseline should raise suspicion of predisposing factors and should lead to the reconsideration of the benefit:risk ratio for its use [68,69]. Overall, if a patient has a viral infection, using antibiotics would increase the risk of side effects when there are no benefits (risks > benefits); if a patient has an indication to receive an antibiotic, azithromycin or levofloxacin may be utilized, but providers need to understand the potential risks. The *JAMA* article demonstrates that, even with an increase in myocardial infarctions, the azithromycin mortality was lower (benefits > risks). Finally, additional research is needed to clarify the discordant research findings and to identify if the risk is true, and if so, what patients are at highest risk. In the meantime, azithromycin and levofloxacin could be used when needed, but the potential risks must be understood.

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### Article highlights

- In 2012, the FDA released a statement to warn healthcare professionals regarding the azithromycin-induced potential QT prolongation and fatal torsades de pointes. The warning included a statement that the risks of cardiovascular death associated with azithromycin were similar to levofloxacin.
- Concerns about cardiac effects from azithromycin and levofloxacin emerged after two retrospective studies evaluating azithromycin and levofloxacin. However, azithromycin, the most frequently used antibiotic, is reported to be less likely than other macrolides to cause QT prolongation and cardiac arrhythmias.
- Studies evaluating the cardiovascular risk of azithromycin and levofloxacin are controversial.
- Decisions regarding the initiation of azithromycin and levofloxacin should be made on a case-by-case basis. When a patient has an indication for either of these two drugs, clinicians should not be reluctant to prescribe them. However, the decision to initiate azithromycin or levofloxacin treatment should be based on a careful evaluation of the preexisting comorbidities, risk factors of QT prolongation and concomitant medication use.
- Risk factors for QT prolongation include hypomagnesemia, hypokalemia and concomitant administration of QT-prolonging drugs. However, there is no 'safe' QT prolongation, even though the lesser the potassium blockade, the rarer is the risk.
- If the QT interval gets over 500 ms, patients should be dutifully monitored until the ECG gets back to normal. A QTc increase > 480 or 60 ms from baseline should raise suspicion of predisposing factors and should lead to the reconsideration of the benefit:risk ratio for its use.

This box summarizes key points contained in the article.

Table 1

Observational studies assessing cardiac risks in azithromycin and levofloxacin.

Drug	Author (year)	Setting	Outcome	Age	Population	Duration	Comparator	Estimate
Azithromycin	Ray <i>et al.</i> (2012) [6]	Cohort	Cardiovascular death	30–74	Medicaid	1–5 days	No antibiotic	HR = 2.88 (1.79, 4.63)
						6–10 days	No antibiotic	HR = 0.88 (0.43, 1.80)
						1–5 days	Amoxicillin	HR = 2.49 (1.38, 4.50)
						6–10 days	Amoxicillin	HR = 0.95 (0.44, 2.06)
						1–5 days	Ciprofloxacin	HR = 3.49 (1.32, 9.26)
						1–5 days	Levofloxacin	HR = 1.27 (0.66, 2.47)
Levofloxacin	Svanström <i>et al.</i> (2013) [10]	Cohort	Cardiovascular death	18–64	General	1–5 days	No antibiotic	RR = 2.85 (1.13, 7.24)
						6–10 days	No antibiotic	RR = 1.44 (0.46, 4.54)
						10–35 days	No antibiotic	RR = 0.69 (0.41, 1.17)
						1–5 days	Penicillin V	RR = 0.93 (0.56, 1.55)
						6–10 days	Penicillin V	RR = 0.75 (0.34, 1.62)
						10–35 days	Penicillin V	RR = 0.92 (0.60, 1.42)
Azithromycin	Rao <i>et al.</i> (2014) [7]	Cohort	Cardiac arrhythmia	30–74	Veterans	1–5 days	Amoxicillin	HR = 1.77 (1.20, 2.62)
						6–10 days	Amoxicillin	HR = 1.37 (0.91, 2.05)
						1–5 days	Levofloxacin	HR = 0.73 (0.47, 1.13)
						6–10 days	Levofloxacin	HR = 0.78 (0.48, 1.26)
						1–5 days	Other antibiotics	OR = 1.01 (0.98, 1.05)
						6–10 days	Other antibiotics	OR = 0.99 (0.95, 1.02)
Levofloxacin	Mortensen <i>et al.</i> (2014) [38]	Cohort	Any cardiovascular event	65+	Veterans	1–5 days	Other antibiotics	OR = 1.17 (1.08, 1.25)
						6–10 days	Other antibiotics	OR = 1.01 (0.97, 1.04)
						1–5 days	Azithromycin	HR = 0.79 (0.40, 1.52)
						1–5 days	Amoxicillin	HR = 1.99 (0.93, 4.23)
						6–10 days	Amoxicillin	HR = 1.07 (0.44, 2.59)
						1–5 days	Amoxicillin	HR = 2.43 (1.56, 3.79)
Cardiac arrhythmia	Rao <i>et al.</i> (2014) [7]	Cohort	Cardiac arrhythmia	30–74	Veterans	6–10 days	Amoxicillin	HR = 1.75 (1.09, 2.82)
						1–5 days	Azithromycin	HR = 1.37 (0.88, 2.13)
						6–10 days	Azithromycin	HR = 1.28 (0.79, 2.08)

HR: Hazard ratio; OR: Odds ratio; RR: Rate ratio.