

# CARDIOVASCULAR SAFETY OF MACROLIDE AND FLUOROQUINOLONE ANTIBIOTICS: AN ANALYSIS OF THE WHO DATABASE OF ADVERSE DRUG REACTIONS

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## Introduction

Macrolides and fluoroquinolones are used worldwide since decades. However, new safety concerns arising from recent case reports and observational studies have suggested a possible association between the exposure to these drugs and the onset of cardiovascular adverse reactions (Svanström et al., 2014)(Ray et al., 20012). To date, results were sometimes conflicting. The aim of the present study is to provide the contribution of real-life data onto the ongoing discussion about cardiovascular toxicity of both macrolides and fluoroquinolones by a disproportionality analysis of data from Vigibase, the WHO database of spontaneous Adverse Drug Reactions (ADRs) reporting.

## Methods

Data were retrieved from Vigibase until 31st May 2016. Macrolides and fluoroquinolones were compared to amoxicillin, as a class and individual drugs, by using the Reporting Odds Ratio (ROR) (with 95% CIs and  $p$  value  $\leq 0.05$ ) to assess the strength of the potential drug-reaction association. Medical Dictionary for Regulatory Activities (MedDRA) was used to classify ADRs. Only ADRs belonging to the System Organ Class 'cardiac disorders' and 'vascular disorders' were considered. Furthermore, it was verified whether the specific MedDRA\_PT was acknowledged in the Summary of Product Characteristics (SPC) of the corresponding drug. Macrolides were then assessed versus fluoroquinolones to clarify which antibiotic class was more prone to causing cardiac ADRs.

## Results

Six thousand eight hundred and ten reports were retrieved; 62% of them were serious and 35% concerned female. For both macrolides and fluoroquinolones, significant RORs for 'Atrial fibrillation' ( $ROR_{\text{macrolides}}=3.03$ , 95%CI 1.63-5.62;  $ROR_{\text{fluoroquinolones}}=2.40$ , 1.31-4.40) and 'Arrhythmia' ( $ROR_{\text{macrolides}}=3.25$ , 1.76-6.01;  $ROR_{\text{fluoroquinolones}}=2.63$ , 1.44-4.81) versus amoxicillin were identified; in addition some disorders of ventricle rhythm reached significance. Furthermore, macrolides showed a significant positive association to 'Bradycardia' ( $ROR=2.93$ , 1.58-5.45) and 'Cardiac arrest' ( $ROR=1.93$ , 1.24-3.02). Analyzing macrolides versus fluoroquinolones, the former resulted more frequently associated with 'Atrial' or 'Ventricular fibrillation' than fluoroquinolones ( $ROR_{\text{atrial-fibrillation}}=1.26$ , 1.02-1.57;  $ROR_{\text{ventricular-fibrillation}}=2.60$ , 1.92-3.54). Azithromycin, clarithromycin and levofloxacin were listed more frequently in association with cardiac ADRs, but also moxifloxacin and ciprofloxacin were often reported.

## **Conclusion**

Beyond the limitations of the study method, these findings highlighted that macrolides and fluoroquinolones could influence cardiac rhythm and induce life-threatening diseases, particularly in patients with underlying cardiovascular risk factors. Although these ADRs seem to be not common, they have a notable impact on clinical practice because of the huge number of the exposed subjects.