Association of macrolide use and cardiac events in patients treated for community acquired pneumonia: post-hoc results from a cluster-randomized cross-over trial

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Introduction

International guidelines advocate the use of macrolide antibiotics as empiric therapy in community-acquired pneumonia (CAP), yet observational studies have related macrolides to an increased risk of cardiac events.[1,2] We examined whether macrolides were associated with cardiac events in patients with CAP during hospitalization.

Objective

To determine whether macrolide use is associated with cardiac complications in patients hospitalised with CAP.

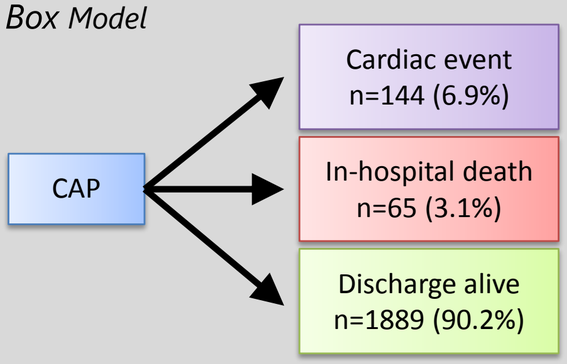
Methods

- Post-hoc analysis of CAP-START study[3]
- Domain: Patients with CAP initially admitted to a non-ICU ward
- Definition of CAP: clinical criteria and/or a new infiltrate
- Excluded: Patients with cardiac complications at the day of hospital admission
- Endpoint: Occurrence of new or worsening arrhythmia, heart failure, and/or myocardial ischemia as reported in discharge letters or medical charts
- Statistical analysis: Competing risk model (see *Box Model*)

ZonMw

CAP START

Box Model



- Arrows modeled by Cox models
- Time-dependent variable for macrolide use
- Patients transferred to other hospital are censored (n=8, 1%)
- Cause-specific (rate) and sub-distribution (net risk) hazard ratio's calculated

Results

- 2,095 patients with diagnosis CAP
- 1,592 (75.9%) with X-ray proven CAP
- Characteristics by macrolide use given in Table 1
- *S. Pneumoniae* most frequent pathogen (15%)

Figure 1 Cardiac events

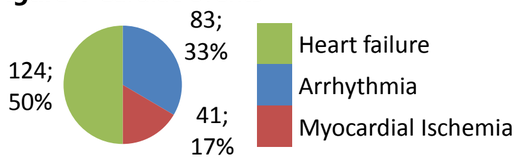


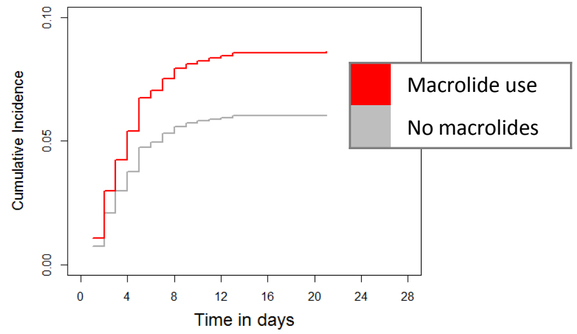
Table 1 Characteristics by macrolide use

Variable	No macrolides n=1451	Macrolide use n=644
Age¶	70 (59;79)	69 (56.75;78)
Male sex	824 (56.8%)	383 (59.5%)
Cardiac disease*	536 (36.9%)	193 (30.0%)
Heart failure	140 (9.6%)	57 (8.9%)
DM	255 (17.6%)	80 (12.4%)
BUN¶	6.5 (4.7;9.2)	6.2 (4.6;9.1)
CRP¶	115 (48;223)	122 (65;218)
Outcomes		
Arrhythmia	34 (2.3%)	19 (3.0%)
Heart failure	54 (3.7%)	45 (7.0%)
Myocardial ischaemia	12 (0.8%)	2 (0.3%)
In-hospital death	38 (2.6%)	27 (4.2%)

*n (%); ¶ median (IQR); * History of cardiac disease; DM Diabetes Mellitus; BUN Blood urea nitrogen; CRP C-reactive protein*

- In the macrolide group, macrolides were started on admission in 500 (77.6%) patients
- 144 (6,9%) patients had cardiac events (Box and Figure 1)
- Cumulative incidence of cardiac event by macrolide use given in Figure 2

Figure 2 Cumulative Incidence



- Cause-specific and sub-distribution hazard ratio's for cardiac events were significantly higher for macrolide use; they increased after multivariate adjustment (Table 2)

Table 2 Hazard ratio's for cardiac event

Macrolide use	CSHR	SDHR
Crude	1.48 (1.06-2.08)	1.60 (1.14-2.23)
*Adjusted**	1.66 (1.18-2.34)	1.81 (1.29-2.55)

*CSHR Cause-specific hazard ratio; SDHR Sub-distribution hazard ratio; * Multivariate adjustment for 17 confounders, specifics available with corresponding author*

Conclusion

In this post-hoc analysis, macrolide use was associated with an increased rate (66%) and net risk (81%) of cardiac events during hospitalization for CAP. This might have led to an increased length of stay, morbidity, and/or mortality.

1. Ray et al; NEJM 2012
2. Schembri et al; BMJ 2013
3. Postma / van Werkhoven et al; NEJM; 2015