Communicating Comprehensive Safety Data Gained from Clinical Trials to the Scientific Community: Opportunities and Difficulties from an Example with Moxifloxacin

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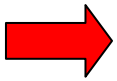
The problem (in general terms)

- Comprehensive safety data assembled from clinical trials (phase I trough 4) and from pharmacovigilance are communicated to Regulatory Authorities
- These rarely appear in detail in publicly available literature (that often focuses mainly on efficacy)
- Yet, even if rare, the corresponding adverse effects are included in the labeling and, as such, must be taken into account by clinicians



This creates

- disconnection between labeling and daily clinical perception
- uneasiness amongst clinicians (who may feel they are shown only the tips of potentially important safety issues).

The specific situation of moxifloxacin

- Moxifloxacin (MXF) is approved in up to 123 countries for major indications (e.g., community-acquired pneumonia [CAP], acute exacerbations of chronic bronchitis [AECB], pelvic inflammatory disease [PID], skin and skin structure infections [SSSI] and complicated intra-abdominal infections [cIAI])
- 140 million prescriptions have been issued for MXF worldwide
- MXF is included as an effective alternative in many guidelines

Beyond known class effects of fluroquinolones, moxifloxacin has been suspected to cause

- **cardiac toxicity** (known 6-10 msec QTc prolongation)
- **hepatotoxicity** (based on rare reports and signals from PSURs).

In 2008, EMA imposed a labelling change:

'*due to safety concerns (hepatic, cardiac [in women and elderly patients], and intestinal problems), moxifloxacin should only be used when other antibiotics cannot be used or have stopped working'*

The approach

- **Objective:** examine and compare the safety profile of MXF *vs* that of the comparators (COMP; all selected as reference therapies), providing unbiased information for comparable clinical situations

- **Method:** in-depth analysis of the manufacturer's clinical trial database for
  - all actively controlled Phase II–IV clinical trials (except one exploratory study)
  - all approved routes of administration and all main indications
  - including patients at risk (hepatic, renal cardiac, age, diabetes, low BMI, …)
  - recording all treatment emergent adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), serious adverse drug reactions (SADRs), premature discontinuations due to AEs, premature discontinuations due to ADRs, AEs with fatal outcome, and ADRs with fatal outcome.
  - coding according to the Medical Dictionary for Regulatory Activities (MedDRA)
  - detection of rare events using Standard MedDRA Queries (SMQs) and customized Bayer Medra queries)
  - descriptive statistics (crude rates), with calculation of relative risk estimates (95% confidence intervals [Mantel–Haenszel analysis stratified by study with constant continuity correction term of 0.1).

Results (1)

- Population:
  - MXF: 14 981 vs. COMP: 15 023)
  - Double blind: ~ 75%
  - IV and IV/PO (sequential): 29%
  - no meaningful difference between MXF and COMP for age, sex, BMI, race, indications, and pre-existing risk factors (renal or hepatic impairment, diabetes mellitus, cardiac disorders, low BMI).
  - distribution mirroring the different main indications (with corresponding risk factors)

Results (2) – global comparisons

A. Double blind studies

Event	Number (%) of patients with treatment					
	PO (N=17,465)		IV/PO (N=3745)		IV (N=1159)	
	MXF (N=8822)	Comp. (N=8643)	MXF (N=1889)	Comp. (N=1856)	MXF (N=588)	Comp. (N=571)
Adverse events (AE)	3782 (42.8)	3711 (42.9)	1202 (63.6)	1138 (61.3)	305 (51.8)	253 (44.3)
Adverse drug reactions (ADR)	2211 (25.0)	2026 (23.4)	455 (24.0)	439 (23.6)	85 (14.4)	83 (14.5)
Serious adverse events (SAE)	318 (3.6)	316 (3.6)	315 (16.6)	282 (15.1)	74 (12.5)	54 (9.4)
Serious adverse drug reaction (SADR)	47 (0.5)	48 (0.5)	53 (2.8)	46 (2.4)	9 (1.5)	7 (1.2)
Premature discontinuation due to AE	366 (4.1)	337 (3.8)	144 (7.6)	131 (7.0)	16 (2.7)	9 (1.5)
Premature discontinuation due to ADR	261 (2.9)	251 (2.9)	74 (3.9)	63 (3.3)	4 (0.6)	4 (0.7)
AE with fatal outcome	28 (0.3)	36 (0.4)	66 (3.4)	54 (2.9)	21 (3.5)	13 (2.2)
ADR with fatal outcome [a]	3 (<0.1)	4 (<0.1)	3 (0.1)	3 (0.1)	0 (0)	1 (0.1)

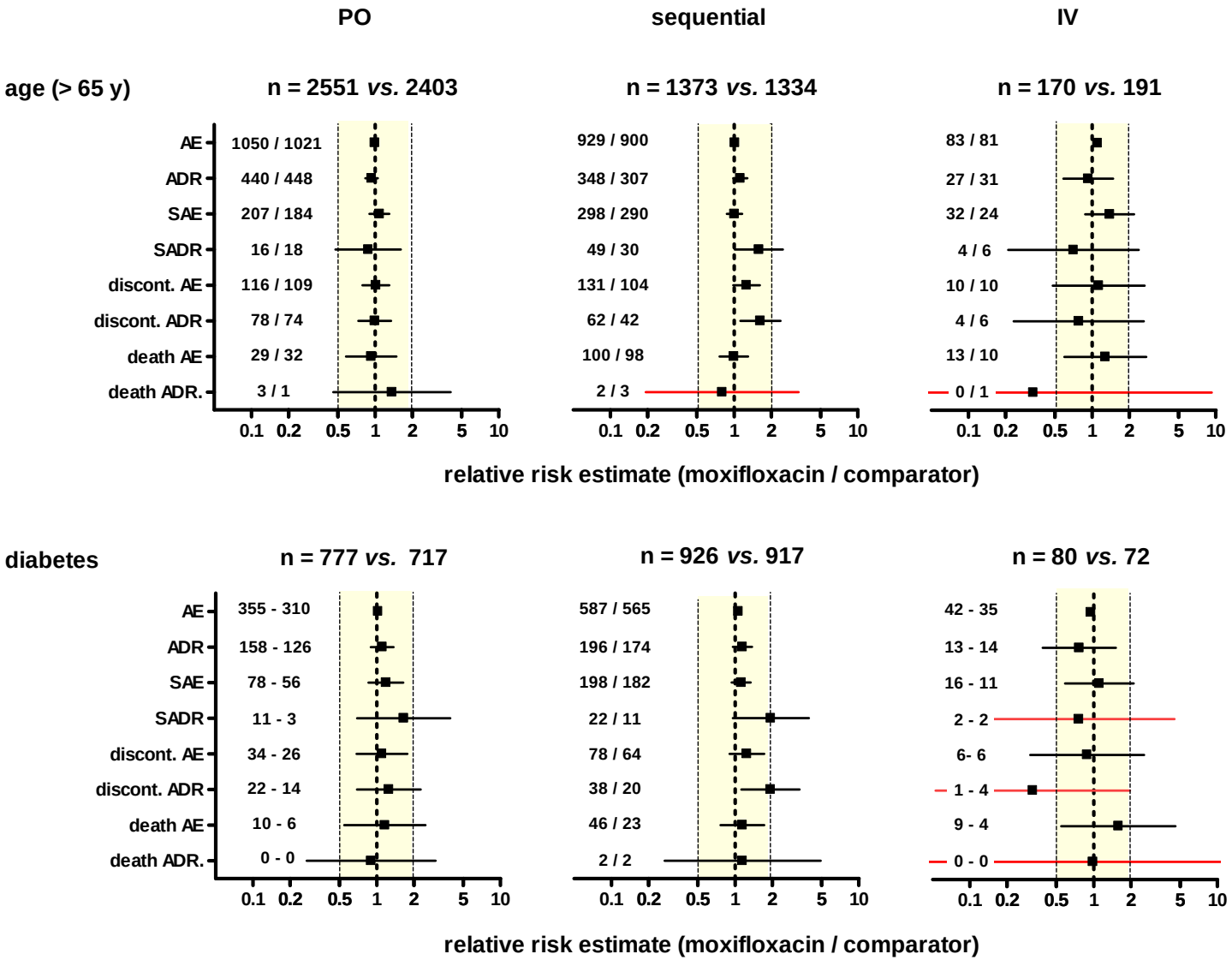
Results (3) - global comparisons

B. Open label studies

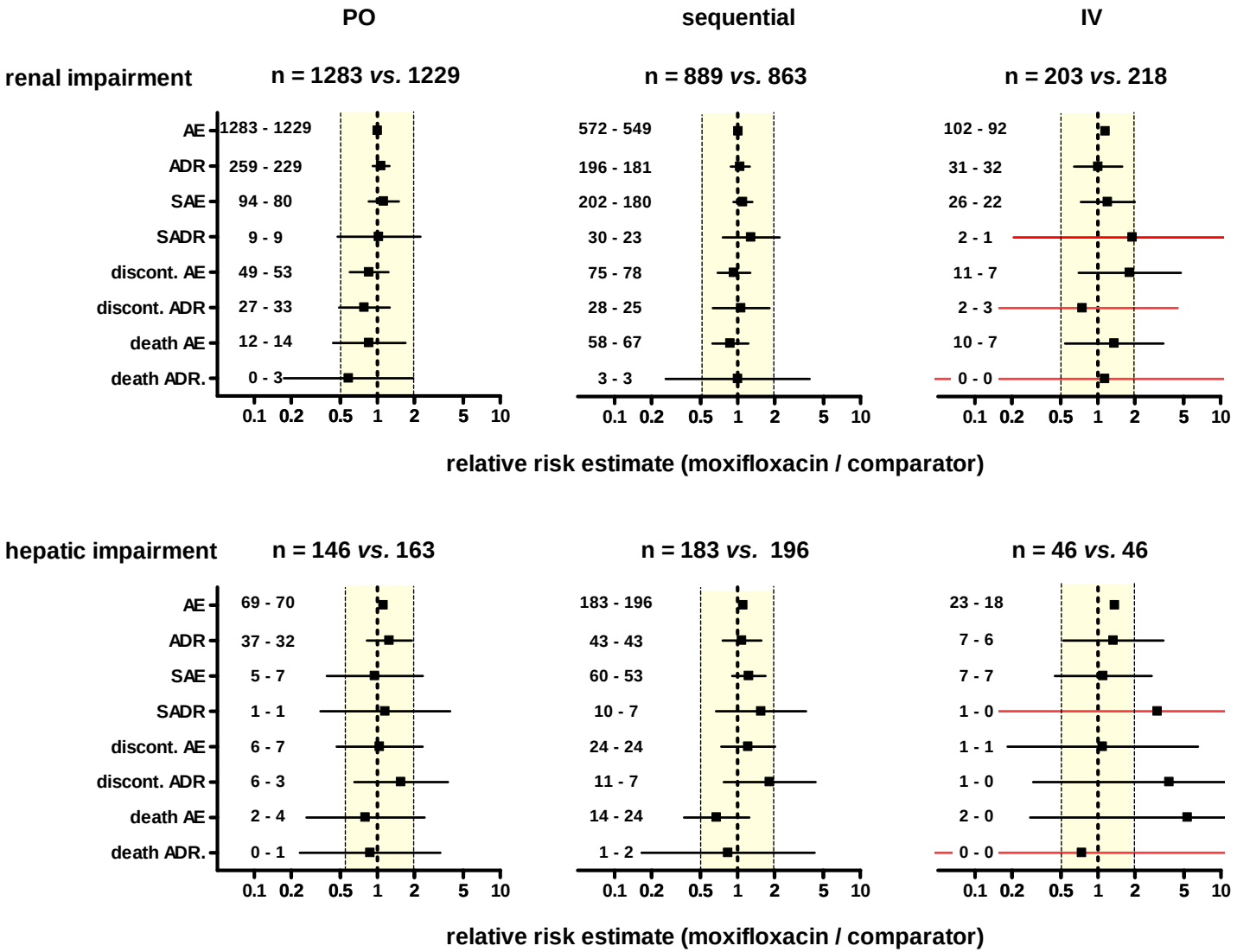
Event	Number (%) of patients with treatment					
	PO (N=3833)		IV/PO (N=3882)		IV (N=701)	
	MXF (N=1791)	Comp. (N=2042)	MXF (N=1542)	Comp. (N=1559)	MXF (N=349)	Comp. (N=352)
Adverse events (AE)	764 (42.7)	766 (37.5)	891 (57.7)	899 (57.6)	86 (24.6)	84 (23.8)
Adverse drug reactions (ADR)	330 (18.4)	325 (15.9)	348 (22.5)	315 (20.2)	49 (14.0)	50 (14.2)
Serious adverse events (SAE)	104 (5.8)	96 (4.7)	280 (18.1)	245 (15.7)	0 (0)	1 (0.2)
Serious adverse drug reaction (SADR)	12 (0.7)	5 (0.2)	42 (2.7)	19 (1.2)	0 (0)	0 (0)
Premature discontinuation due to AE	70 (3.9)	67 (3.2)	137 (8.8)	109 (6.9)	21 (6.0)	11 (3.1)
Premature discontinuation due to ADR	51 (2.8)	49 (2.4)	66 (4.2)	54 (3.4)	17 (4.8)	9 (2.5)
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.1)	80 (5.1)	0 (0)	0 (0)
ADR with fatal outcome [b]	0 (0)	0 (0)	1 (<0.1)	2 (0.1)	0 (0)	0 (0)

- **AE, ADR and SADR were mainly "*gastrointestinal disorders*" and "*changes observed during investigations*" such as asymptomatic QT prolongation).**
- **Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with moxifloxacin and comparators.**

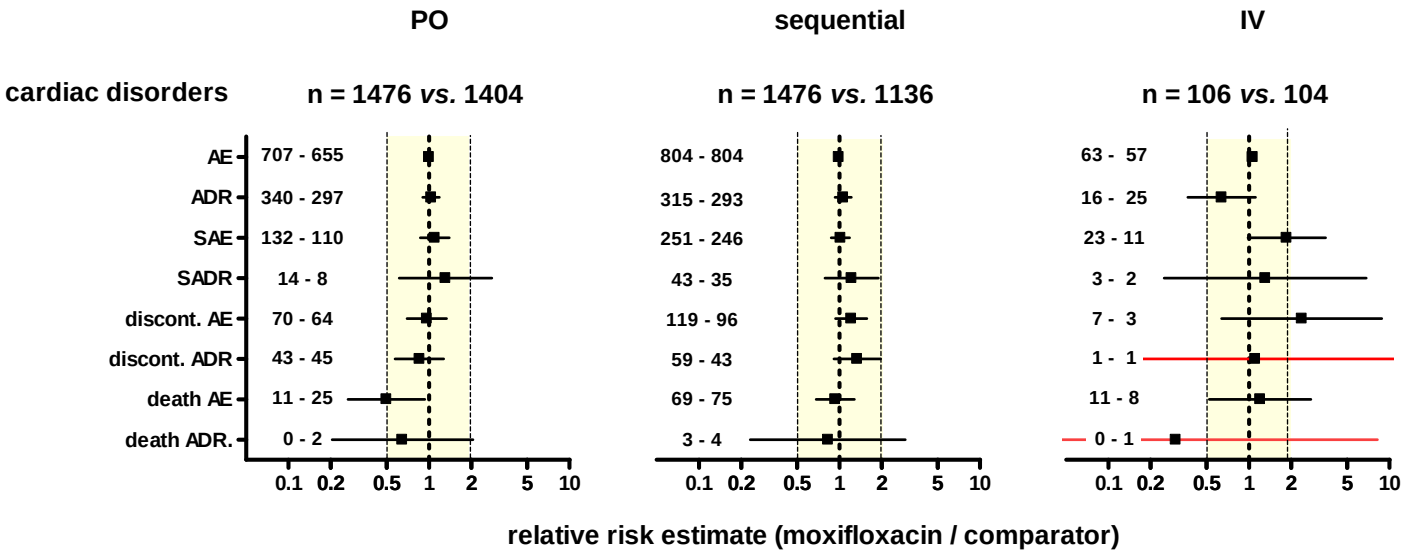
Results (4): patients at risk

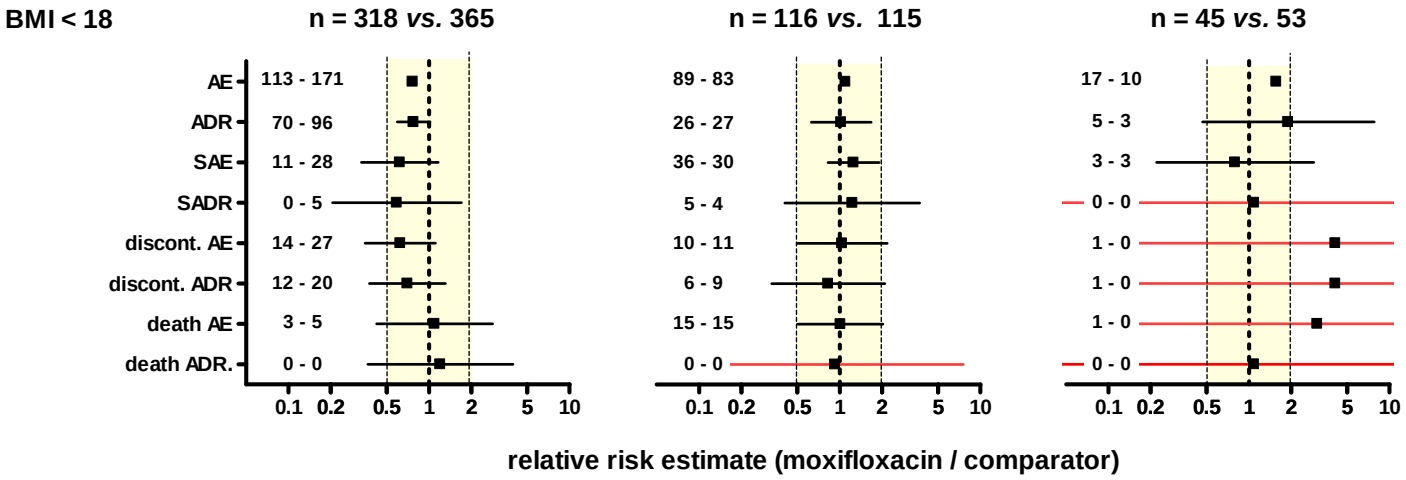


Results (5): patients at risk



Results (5): patients at risk

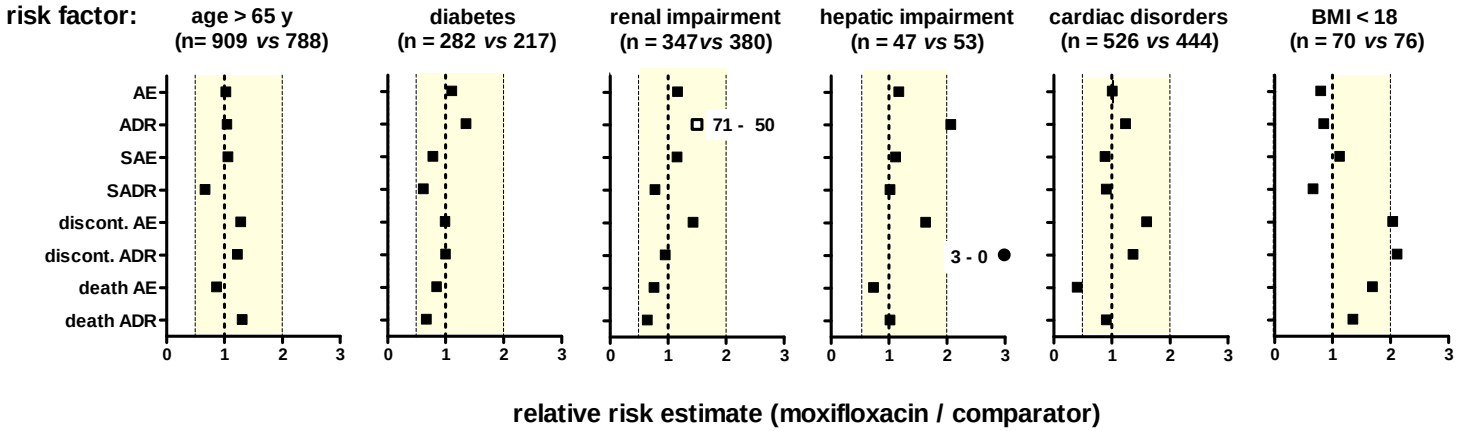




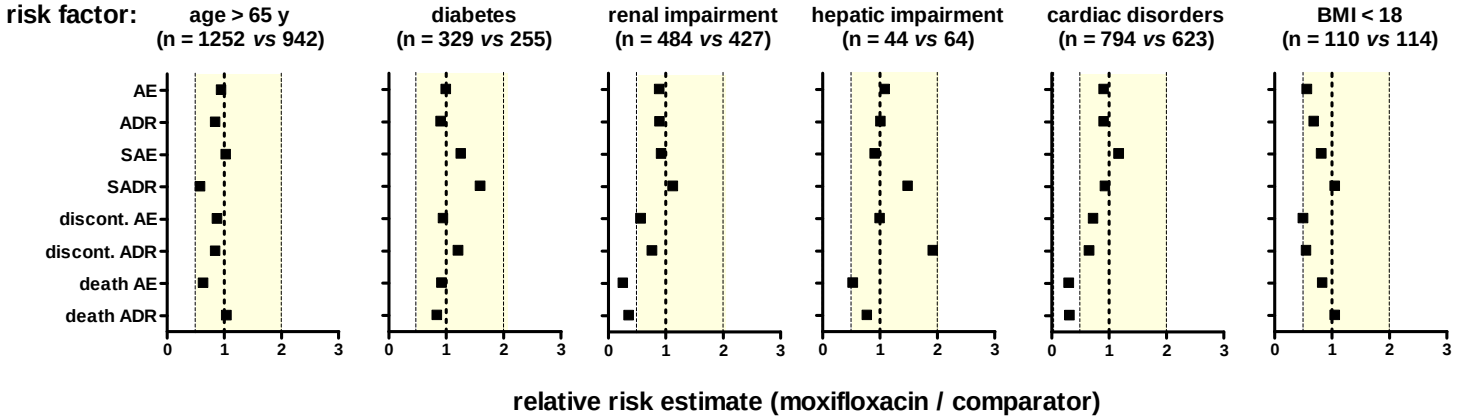
Results (6): drug comparisons

A. oral therapy

1. moxifloxacin *vs* β-lactams



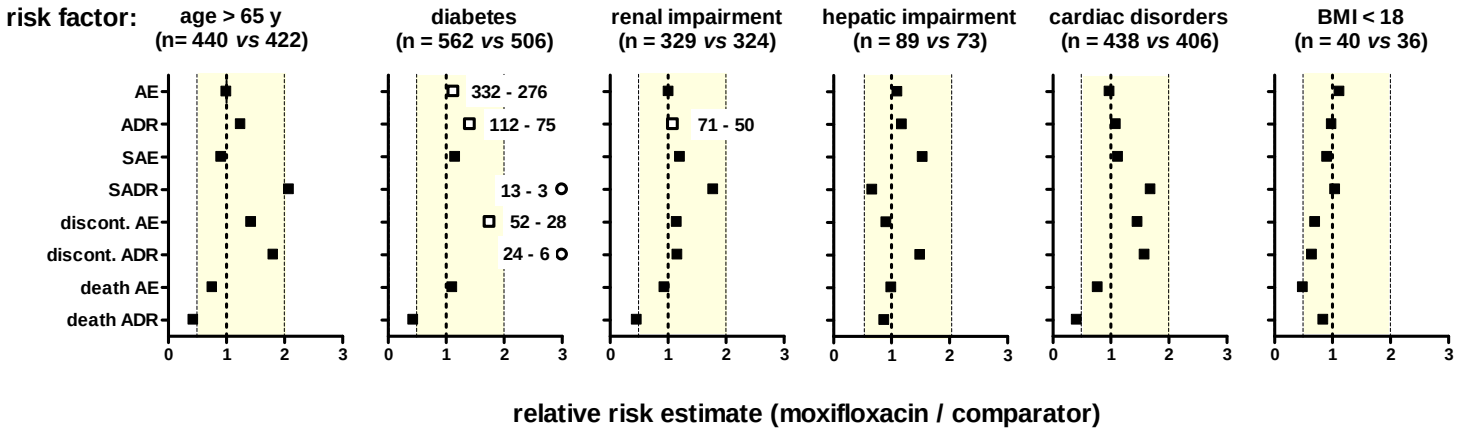
2. moxifloxacin *vs* macrolides



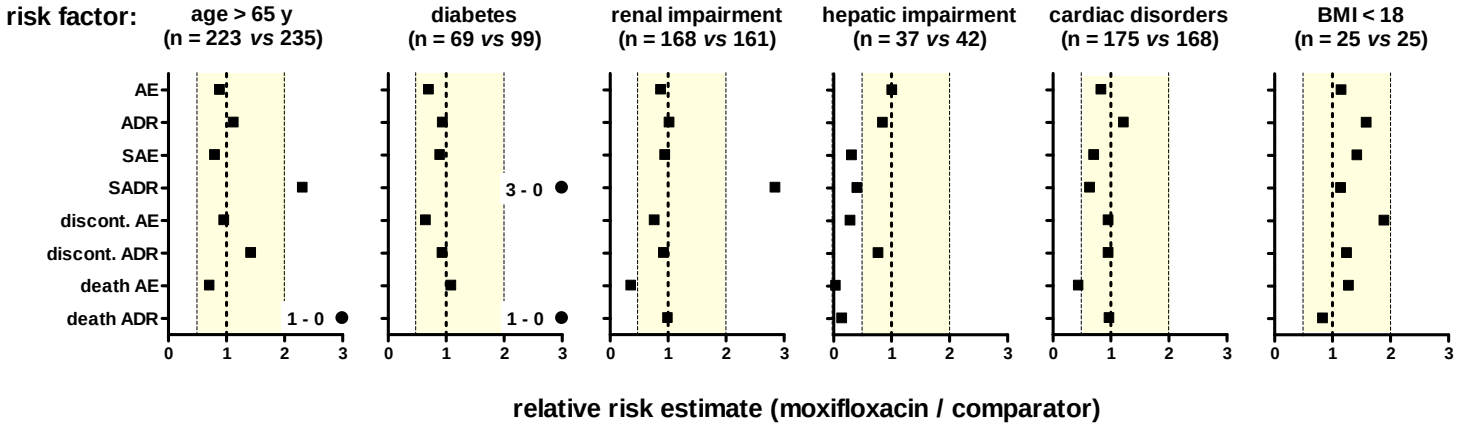
Results (7): drug comparisons

B. sequential therapy

1. moxifloxacin *vs* β-lactam alone



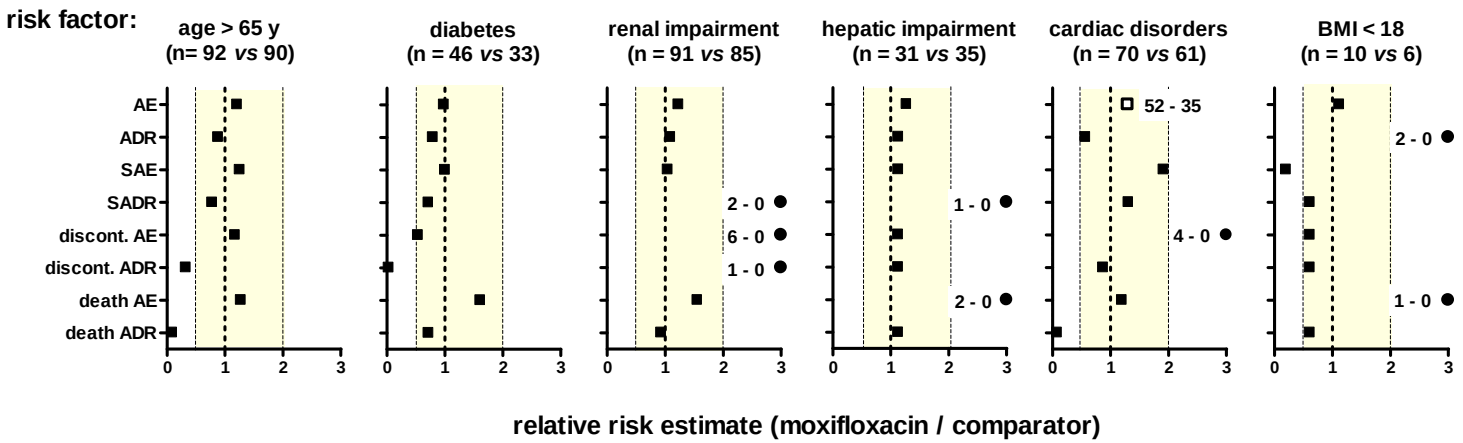
2. moxifloxacin *vs* β-lactam alone or combined with a macrolide



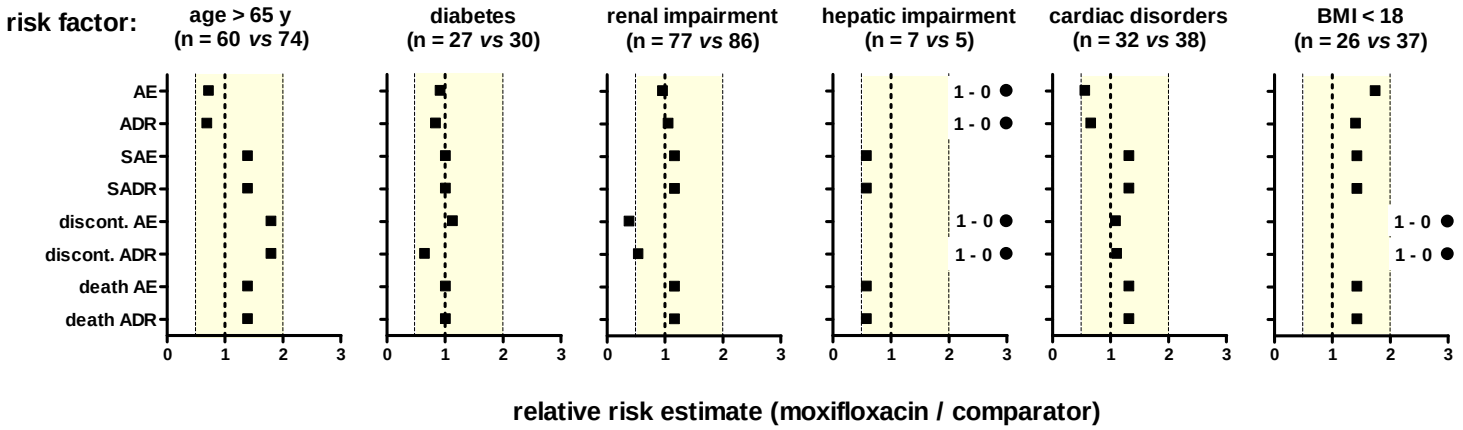
Results (8): drug comparisons

C. intravenous therapy

1. moxifloxacin *vs* β-lactam



2. moxifloxacin *vs* another fluroquinolone



Conclusions (for moxifloxacin)

- The overall safety profile of moxifloxacin was found similar to that of comparators from clinical trials
- More specifically, and with regard to recent questions:
  - Hepatic events reactions were very low and not superior in a statistically significant manner to comparators even if considering patients with hepatic disorders
  - While QTc prolongation were observed, no increase clinical adverse effects were seen even in patients with prexisting cardiac disorders vs. the comparator(s)
  - Specific toxicities (tendonitis, e.g.) remained exceedingly rare with no difference between moxifloxacin and the fluroquinolone comparator
  - Skin events were extremely are and less frequent than with β-lactams

Full details are available from
Tulkens *et al.* Moxifloxacin safety: an analysis of 14 years of clinical data. Drugs R D. 2012 Jun 1;12(2):71-100 (open access).

Pros and Cons of this approach

Pros

- Unbiased (randomized) comparison of treatments with similar indications and target populations (all clinically-valid comparators)
- Estimation of the true incidence of relatively rare effects (equal balance of patients for known and unknown factors)
- Detailed assessment of the detected side-effects and documented causality

Cons

- Populations analyzed potentially not representing the true final populations in which the drug is used
- Patients with known contra-indications excluded by study design
- Number of patients too low to detect very rare effects
- Labor intensive process that can only be undertaken late in drug development and commercialization

This approach may be useful for providing clinicians and regulators with a global analysis of **actual** risk factors for **comparable drugs** in **comparable indications**