Moxifloxacin safety data review

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- founding member and past-President of the International Society of Anti-infective Pharmacology

8. Forschungswerkstatt Moxifloxacin 2011
Leverkusen -- 17./18. November 2011

Einige Wörter…

- Ich bedauere, diese Darstellung nicht auf deutsch geben zu können...
- Die Deutsche Sprache ist jedoch sowohl sehr schön als auch sehr logisch...
- Und ich bin ein begeisteter Zuhörer von J.S. Bach's Passionnen oder Operns von Wagner ...
- Aber ich musste bereits alle Tage Französisch, Flämisch und Englisch sprechen... und Deutsch ist für einen Französigsprachigen schwierig...
- Ich werde versuchen, die Fragen auf deutsch zu verstehen ...

Die Lokalisierung der *Université catholique de Louvain* in Brüssel

Die Gebäude der medizinischen Fakultät und das Krankenhaus

Die Gruppe der Pharmakologie/Toxikologie der Antibiotika

Fluoroquinolone selection: appropriate benefit-risk profiles

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7. Forschungswerkstatt Moxifloxacin 2009
Leverkusen – 26-27 June 2009

Contents of the Presentation

- All antimicrobials have associated toxicity risks …
  - Major non-serious and serious side-effects associated with the main antimicrobials used in the treatment of CAP (β-lactams, macrolides, tetracyclines, fluoroquinolones).
- Adverse effects of moxifloxacin *vs* other agents
  - a comprehensive analysis
- The risk of bacterial failure
  - are guidelines "safe" ?
- Conclusions

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
fluoroquinolones	levofloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • Hematologic toxicity • Hepatotoxicity • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval and isolated cases of torsade de pointes • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

* based on an analysis of the respective labelling (SmPC or equivalent)

Conclusions (# 1):

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the specific environment and for the specific patient

The "end result"

LEADING ARTICLE

Drug Safety 2009; 32 (5): 359-378
0114-5916/09/0005-0359/$49.95/0

Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

Comparison with Other Fluoroquinolones and Other Antibacterial Classes

Françoise Van Bambeke and *Paul M. Tulkens*

Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention to the contraindications and warnings mentioned in the labelling.

Where are we now with moxifloxacin ?

- Hepatotoxicity: is this a real issue ?
- What do the "*whole clinical trial data base*" tells us ?
- Is moxifloxacin still effective ?

Hepatic toxicity of antibiotics

- Usually idiosyncratic (can be associated with other allergic reactions). [1]
- Clavulanic acid: genetic deficiency in glutathione S-transferases ? [2] (longer latency period than other antibiotics…)
- Macrolides: related to reactive metabolites (nitrosoalkanes) that covalently bind to proteins, forming modified antigens (immunoallergic hepatitis) [3]
- Tetracyclines: related to inhibition of mitochondrial β-oxidation of fatty acids [4]
- Fluoroquinolones: remains anecdotal and unpredictable,[1] except for for molecules with substituent-generating reactive intermediates
  - difluoroaniline (temafloxacin and trovafloxacin) [5]
  - cyclopropylamine (trovafloxacin; for which co-exposure to lipopolysaccharide may also be critical) [6]

1. Robles M, Andrade RJ. Rev Esp Quimioter. 2008 Dec;21(4):224-33
2. Lucena et al., Hepatology. 2008 Aug;48(2):588-96.
3. Pessayre et al. J Antimicrob Chemother 1985 Jul; 16 Suppl A: 181-94
4. Freneaux et al. Hepatology 1988 Sep; 8(5): 1056-62
5. Blum et al. Clin Infect Dis 1994 Jun; 18(6): 946-50; Chen et al. N Engl J Med 2000 Feb 3; 342(5): 359-60; Lucena et al. Clin Infect Dis 2000 Feb; 30(2): 400-1
6. Sun et al. Chem Res Toxicol 2008 Mar; 21(3): 711-9
7. Shaw et al. Toxicol Sci. 2009 Jan;107(1):270-80

Patients with possible drug-related hepatic disorders in comparative clinical trials (oral moxifloxacin)

	Moxifloxacin (N=9394)			Comparators (N=9359)		
	AE [ADR]					
(Sub-)SMQ	Total	Serious	Fatal	Total	Serious	Fatal
Comprehensive search All cases	219 (2.3%) [153 (1.6%)]	6 (<0.1) [3 (<0.1)]	0 [0(–)]	223 (2.4%) [139 (1.5%)]	8 (<0.1%) [3 (<0.1%)]	2 (< 0.1%) [0 (–)]
Liver-related investigations, signs and symptoms *	180 [120]	4 [2]	0 [0]	198 [124]	4 [1]	0 [0]
Cholestasis and jaundice of hepatic origin	13 [9]	0 [0]	0 [0]	6 [4]	1 [1]	0 [0]
Possible liver-related coagulation and bleeding disturbances	17 [15]	0 [0]	0 [0]	13 [8]	1 [1]	0 [0]
Possible drug-related hepatic disorders - severe events only	**19 [16]**	**2 [1]**	0 [0]	**17 [7]**	**3 [0]**	0 [0]
Hepatitis, non-infectious	7 [7]	1 [1]	0 [0]	6 [3]	0 [0]	0 [0]
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	12 [9]	1 [0]	0 [0]	9 [4]	1 [0]	0 [0]
Liver neoplasms, benign	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Liver neoplasms, malignant and unspecified	0 [0]	0 [0]	0 [0]	2 [0]	2 [0]	0 [0]

AE: adverse event; ADR: adverse drug reaction; SMQ: Standard MedDRA Query
The allocation of a liver-related adverse event to any of the sub-SMQs is not mutually exclusive. One patient can have one event allocated to several sub-SMQs, or several events located to different sub-SMQs. In consequence, the overall number of patients identified with the "comprehensive search" is smaller than the sum of all patients allocated to the sub-SQMs.

*** similar to published studies**

Bayer HealthCare
Bayer Schering Pharma

SMQ-search for "severe events": Hepatic overview by event type/diagnosis

	Moxifloxacin AE [ADR]	Comparator AE [ADR]
Total	**19 [16]**	**17 [7]**
Hepatitis		
CTC grade ≥3 (severe)	3 [2]	1 [0]
CTC grade <3 (non-severe)	4 [4]	5 [3]
Hepatic failure		
CTC grade ≥3 (severe)	1 [0]	0
CTC grade <3 (non-severe)	2 [2]	1 [1]
Liver disorder		
CTC grade ≥3 (severe)	0	3 [1]
CTC grade <3 (non-severe)	9 [8]	5 [2]
Liver neoplasm	0	2 [0]
Outcomes		
Resolved/improved	17	10
Unchanged	1	2
Worsened/death	0	1
Unknown	1	4

AE: adverse event; ADR: adverse drug reaction

Common Terminology Criteria for Adverse Events v3.0:

- AP, GGT, AST, ALT: Grade 1 (mild), >ULN – 2.5x ULN; Grade 2 (moderate), >2.5 – 5.0x ULN; Grade 3 (severe), >5.0 – 20.0x ULN; Grade 4 (life-threatening), >20.0x ULN
- Total bilirubin: Grade 1 (mild), >ULN – 1.5x ULN; Grade 2 (moderate), >1.5 – 3.0x ULN; Grade 3 (severe), >3.0 – 10.0x ULN; Grade 5 (life-threatening), >10.0x ULN

Crude incidence rates of acute liver injury caused by antibiotics *

Antibiotic	population	Incidence rate (CI)		endpoint	reference
		per 100,000 users	per 100,000 prescriptions		
fluoroquinolones (w/o moxifloxacin)	Outpatient clinic, Sweden (1995-2005)	0.7 (0.5-1.1)		International consensus	[1]
moxifloxacin	Outpatient clinic, Sweden (1995-2005)	0.08 (0.0-0.5)		International consensus	[1]
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)	4.9 (0.9-27.6)	International consensus, hospitalisation	[2]
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)	14.0 (4.8-41.2)	International consensus, hospitalisation	[2]
amoxicillin-clavulanic acid	General practice research database, United Kingdom (1991-1992)	22.5 (14.7-34.4)	17.4 (11.4-26.5)	International consensus	[3]

* see Van Bambeke & Tulkens, Drug Safety (in press) for full Table and details

1. De Valle et al. Aliment Pharmacol Ther 2006 Oct 15; 24(8): 1187-95
2. Perez et al. Epidemiology 1993 Nov; 4(6): 496-501
3. Garcia-Rodriguez et al. Arch Intern Med 1996 Jun 24; 156(12): 1327-32

An extensive review

J Antimicrob Chemother 2011; **66**: 1431–1446
doi:10.1093/jac/dkr159 Advance Access publication 17 May 2011

Journal of Antimicrobial Chemotherapy

Hepatic safety of antibiotics used in primary care

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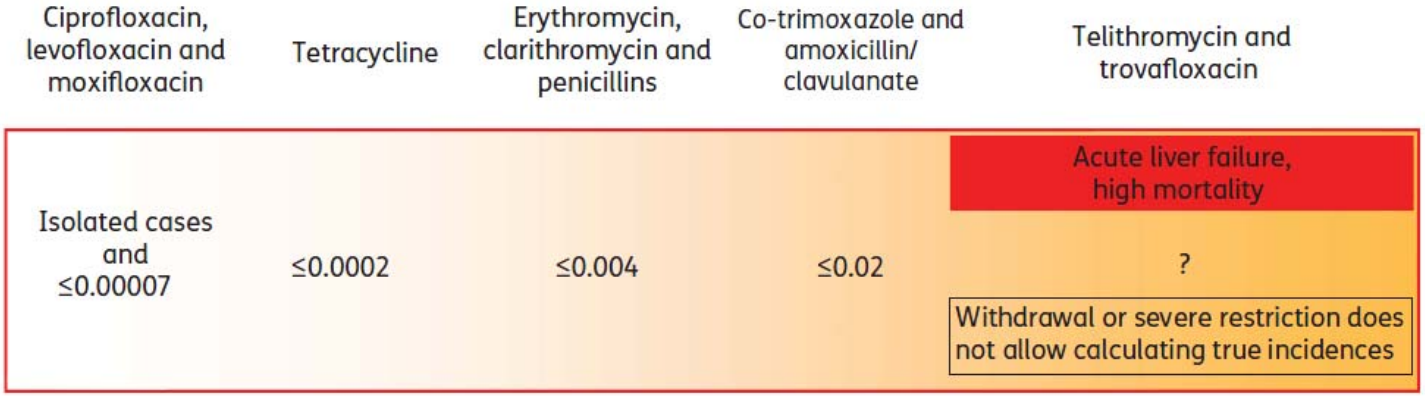

Figure 1. Hepatotoxicity risk of antibiotics (percentage of prescriptions for antibiotics with main indications for use in the community setting). Derived from references 32, 37, 40, 42, 44, 73, 89, 96 and 108. Excluding antibiotics used mainly for the treatment of tuberculosis.

An extensive review

J Antimicrob Chemother 2011; **66**: 1431-
doi:10.1093/jac/dkr159 Advance Access

Hepatic safety

Ra

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Moxifloxacin

Frequency

Reviews of clinical trials and post-marketing surveillance studies indicate minimal incidence of hepatic injury, though liver function tests may be abnormal in ~1%–5% of patients.[115,116]

While no index case of moxifloxacin-related liver injury has emerged in either clinical trials or post-marketing surveillance, and published data have remained scanty for many years,[117,118] there have been spontaneous reports of hepatocellular injury.

These include eight deaths due to hepatic failure where a link to moxifloxacin could not be excluded[119] and a more recent case where it was considered to be idiosyncratic.[120]

This has been introduced as an amendment by the EMA in the European SPC,[121] but such fatal cases should be seen in the context of 85 million treatments with moxifloxacin worldwide at that time.[122]

The current, revised SPC mentions elevation of transaminases as being common, hepatic alteration uncommon, and icterus and hepatitis rare. Moxifloxacin is not included in the list of drugs identified in at least five adjudicated cases of DILI.[123] Moxifloxacin, as for levofloxacin, was also found to cause no additional hepatotoxicity when used by patients with hepatitis induced by first-line antituberculosis drugs.[99]

Moxifloxacin hepatotoxicity (confirmation)

- There is no evidence from currently available data that reactions are more frequent than with comparators
  - Clinical trials:
    - Apparent imbalance in drug-related “severe events” detected in the EU Periodic Safety Report was based on clinically non-severe, non-serious events (the number of serious, or clinically severe ADRs is too small for meaningful conclusions)
  - Spontaneous and registry data:
    - all data show a lower incidence for fluoroquinolones *vs* macrolides and amoxicillin/clavulanic acid
    - No signal in EBGM analysis conducted by FDA in 2006

The whole clinical trial data base

The whole clinical trial data base

22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
31.03.2012 - 03.04.2012

Author data	P. Tulkens*, P. Arvis, F. Kruesmann (Brussels, BE; Loos, FR; Wuppertal, DE)
Title	**Clinical Safety of Moxifloxacin (MFX): an Analysis of "Valid for Safety" Data from Controlled Phase II to Phase IV Studies Performed between 1996 and 2010**
Topic	34. Antimicrobial clinical trials

Submitted on 14 November 2011

For submission to ***Drug Safety*** as **Original Research Article**

A. Title

Moxifloxacin safety: an analysis of 14 years of clinical data

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[2]Bayer Schering Pharma, Loos, France.

[3]Bayer Schering Pharma, Wuppertal, Germany

Which patients and which comparators ?

Comparators	Patients (no.)					
	PO (N=21,298)		IV/PO (N=6846)		IV only (N=1860)	
	Moxifloxacin (N=10613)	Comparators (N=10685)	Moxifloxacin (N=3431)	Comparators (N=3415)	Moxifloxacin (N=937)	Comparators (N=923)
A. Double-blind studies						
β-lactams	2391	2104	1077	1034	408	390
β-lactams + macrolides	274	155	0	0	0	0
Fluoroquinolones	2246	2287[a]	444	457[b]	0	0
Macrolides	3659	2929	0	0	00	0
Other	1230	1168[c]	368	365[d]	180	181[e]
Total	**8822[h]**	**8643**	**1889**	**1856**	**588**	**571**
B. Open-label studies						
β-lactams	1318	1301	578	574	0	0
β-lactams + macrolides	186	190	0	0	0	0
β-lactams ± macrolides	0	0	532	549	0	0
Fluoroquinolones	263	270[f]	349	352[f]	349	352[f]
Macrolides	287	281	0	0	0	0
Other	0	0	456	463[g]	0	0
Total	**1791[h]**	**2042**	**1542**	**1559**	**349**	**352**

open-label and double-blind actively controlled clinical trials included in the clinical trial database of moxifloxacin 400 mg once-daily performed by the registration holder (currently Bayer HealthCare) as part of the phase II-IV programmes initiated, completed and with raw data reported to the sponsor between 1996 and 2010

Which global results ?

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)

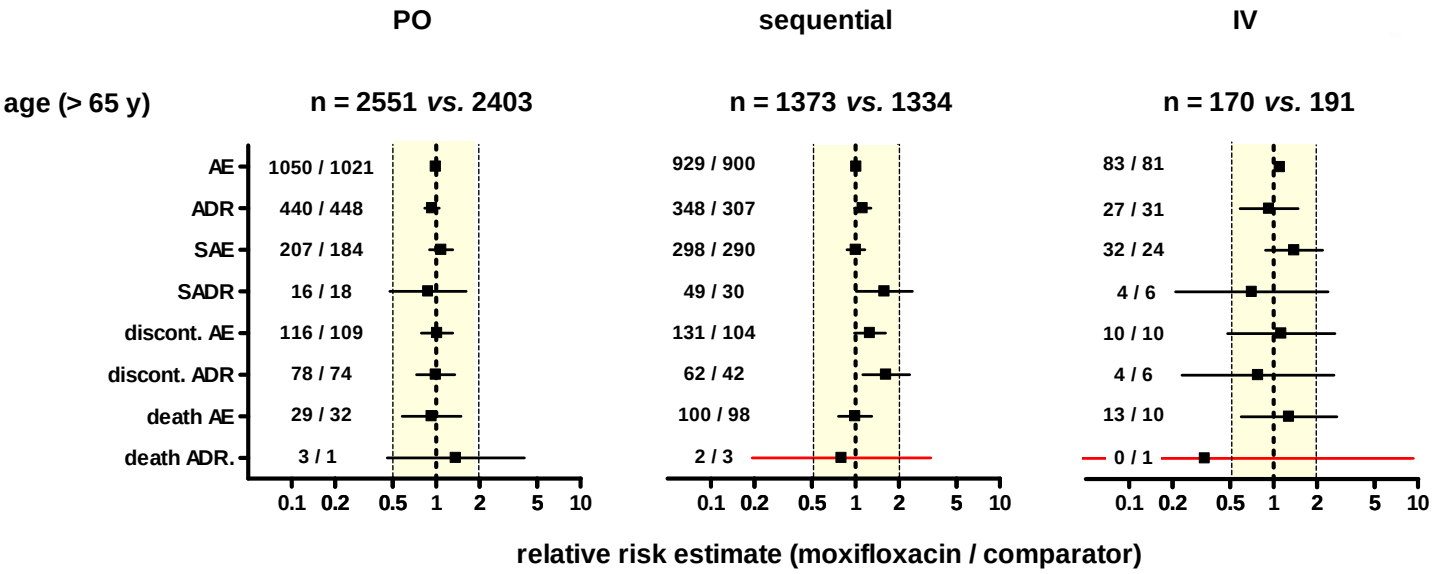
Which global results ?

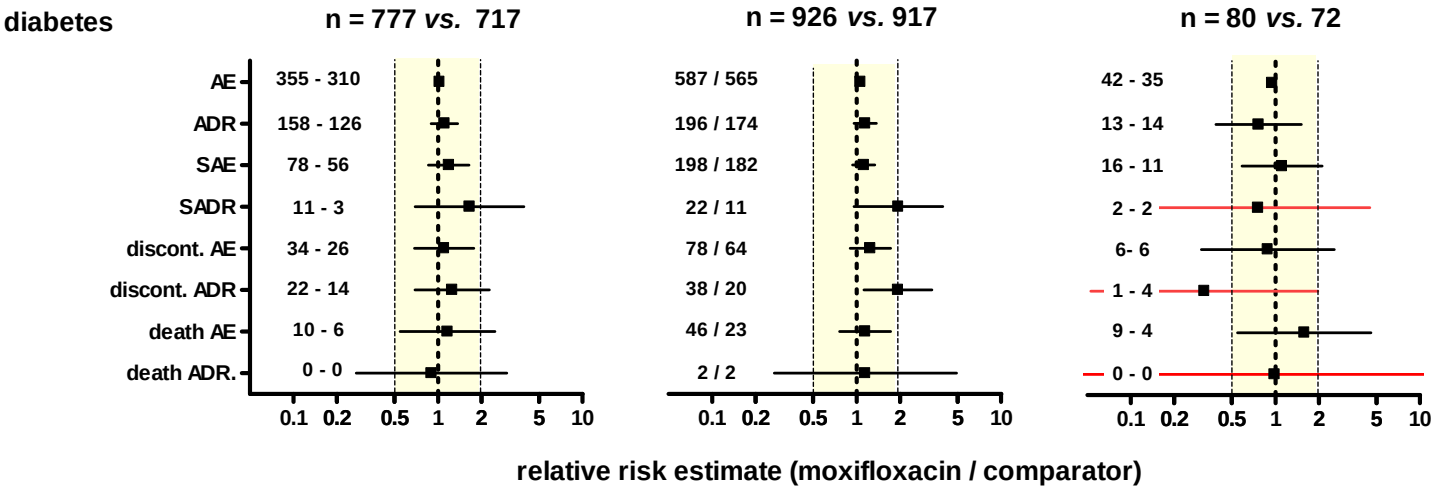
B. Open label studies

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)

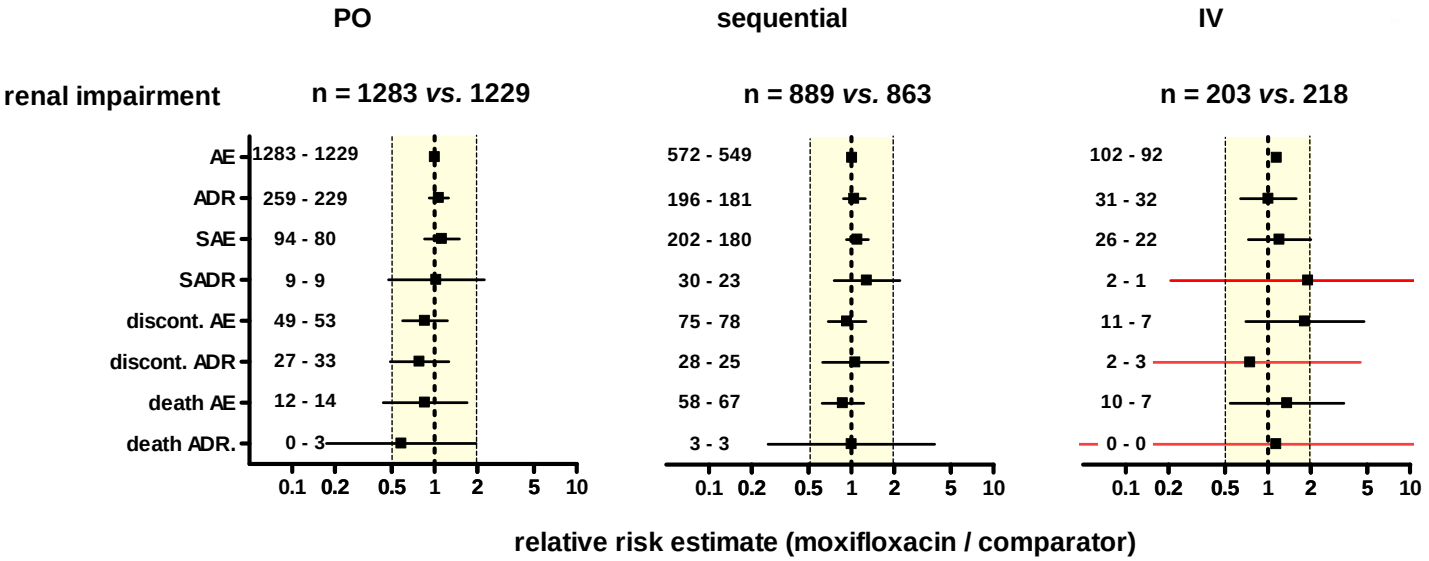
- **AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation).**
- **Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated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

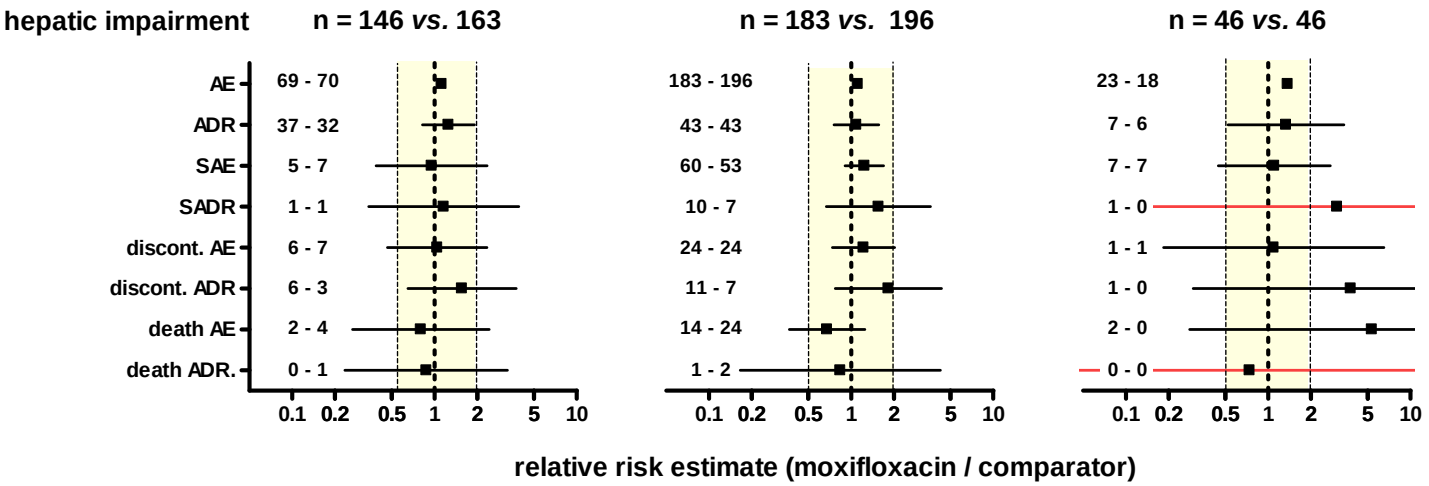
And for patients at risk ?



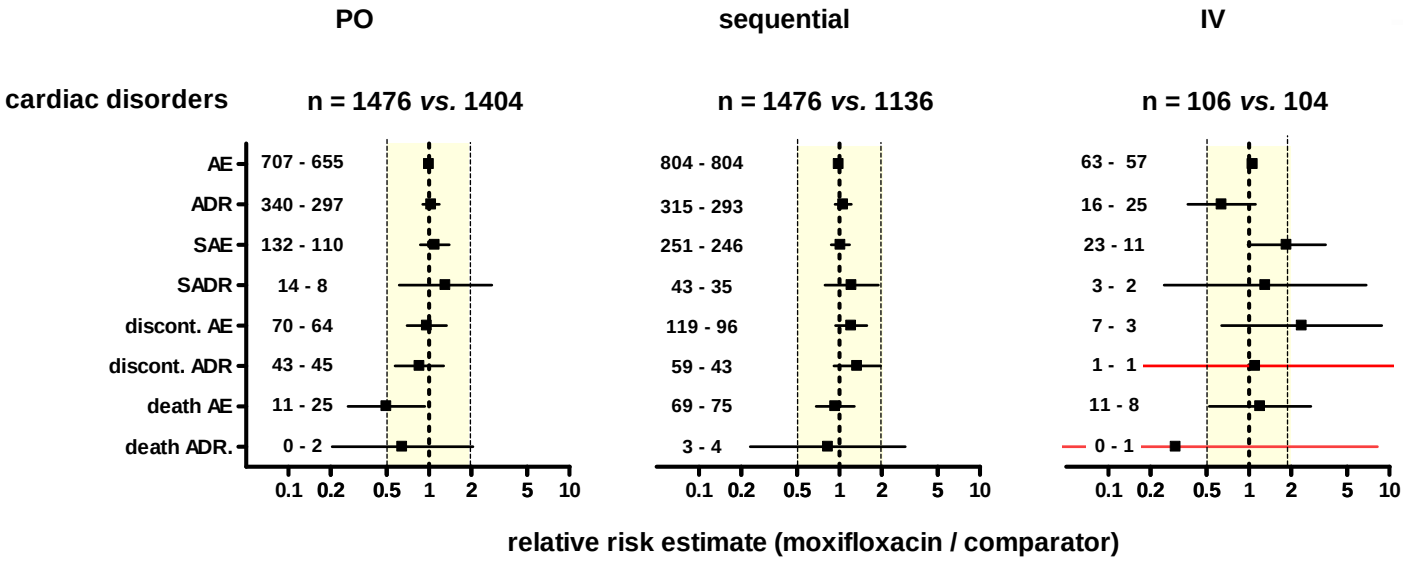


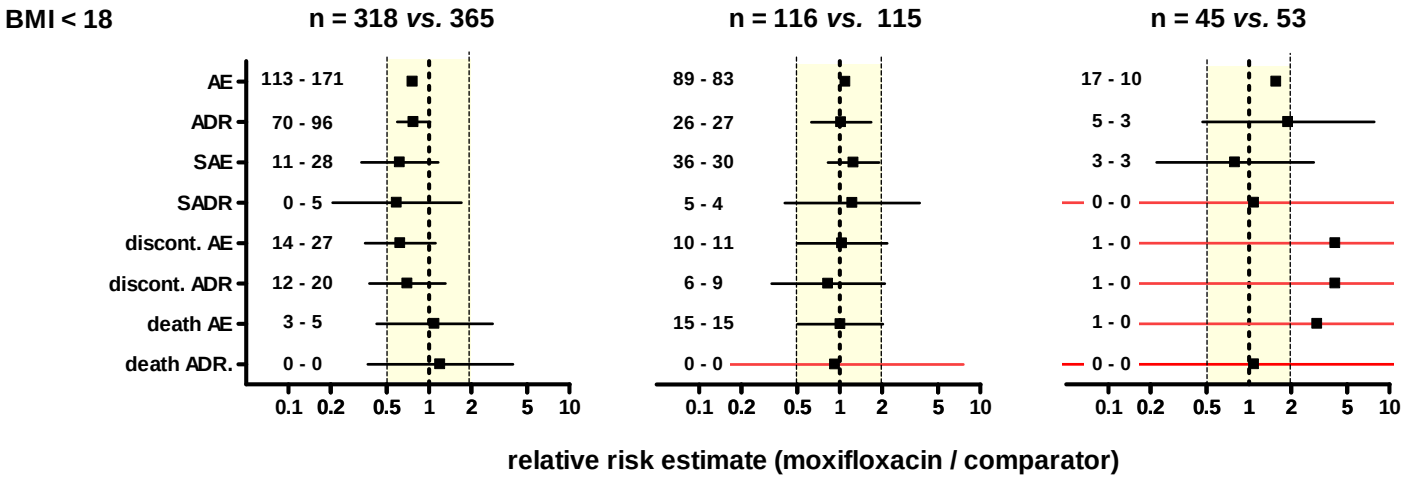
And for patients at risk ?





And for patients at risk ?

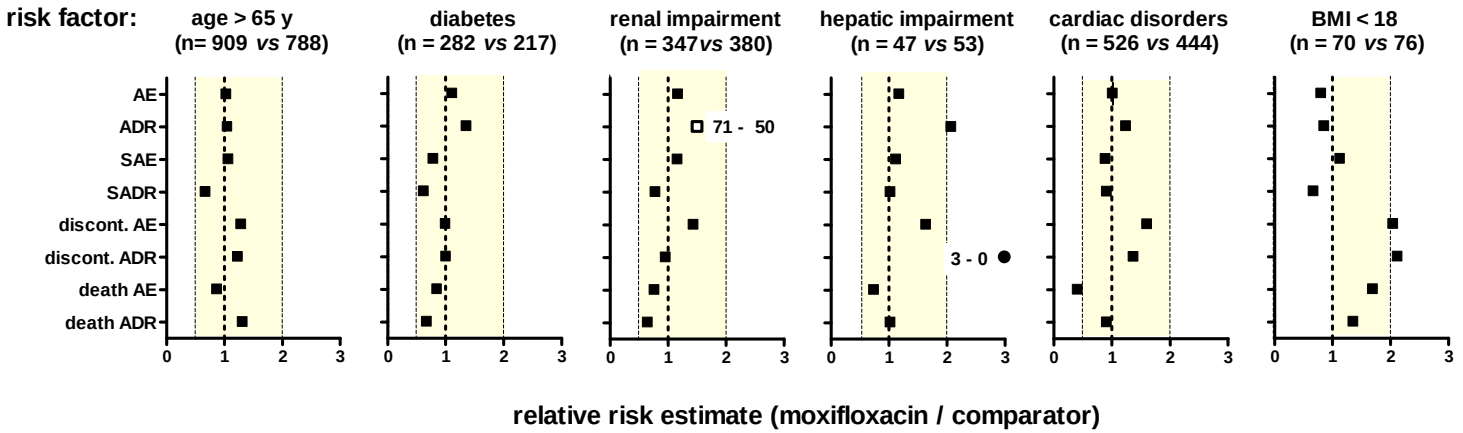




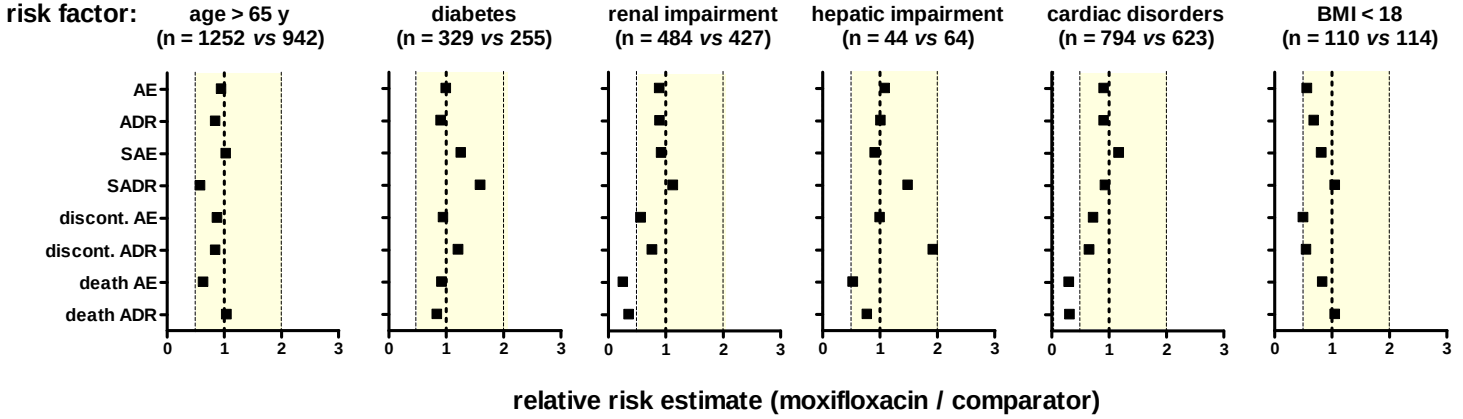
And what if we compare drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



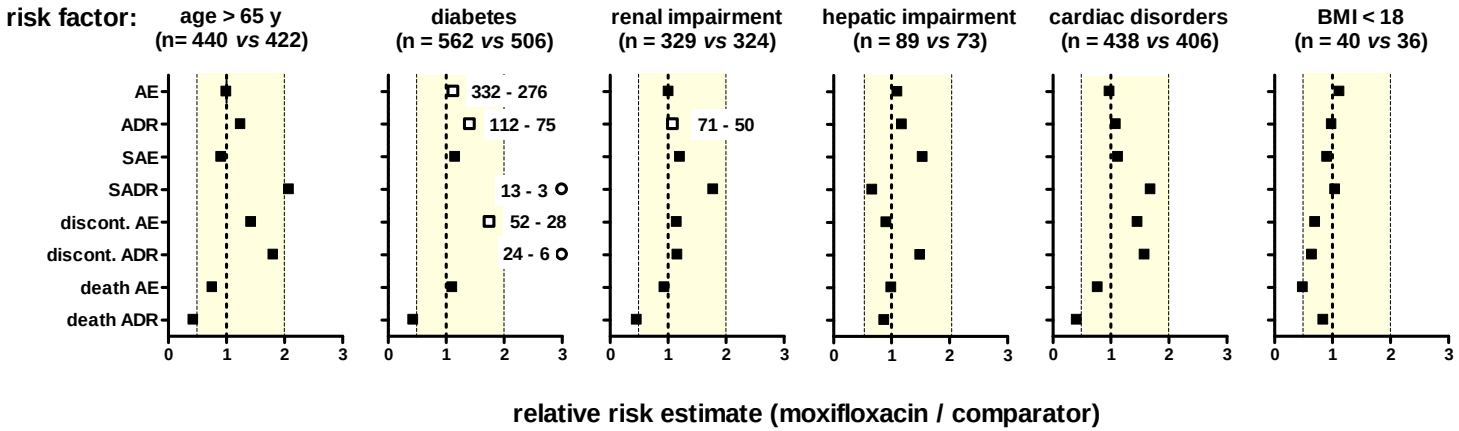
2. moxifloxacin *vs* macrolides



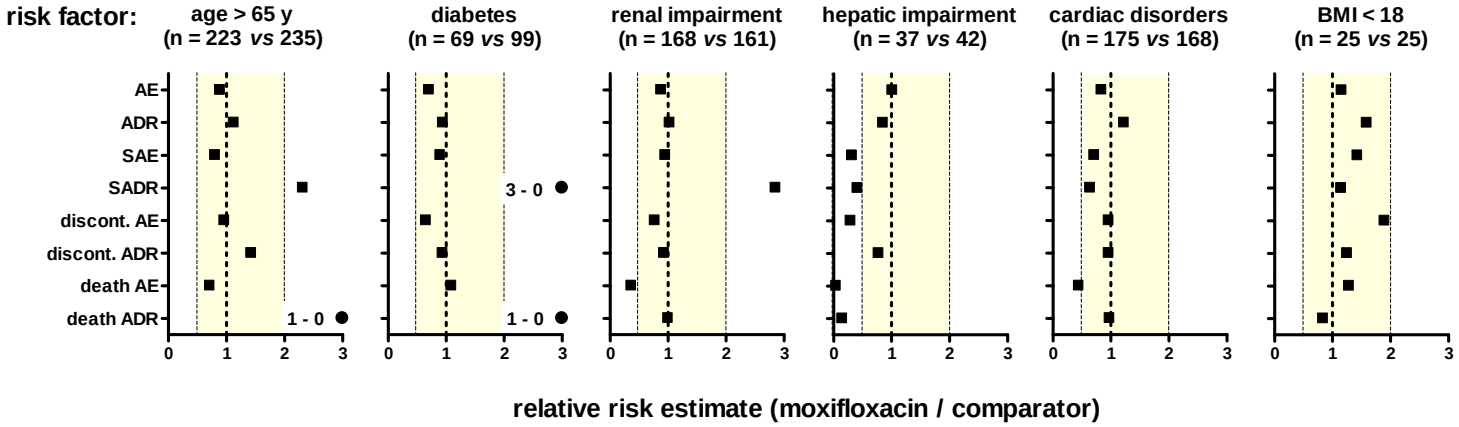
And what if we compare drugs ?

B. sequential therapy

1. moxifloxacin *vs* β-lactam alone



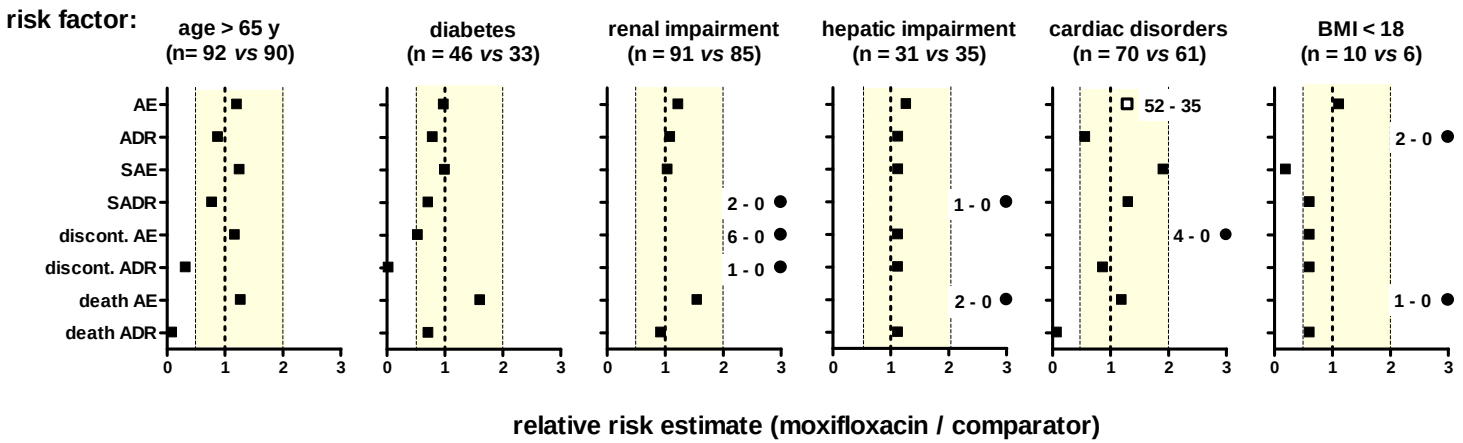
2. moxifloxacin *vs* β-lactam alone or combined with a macrolide



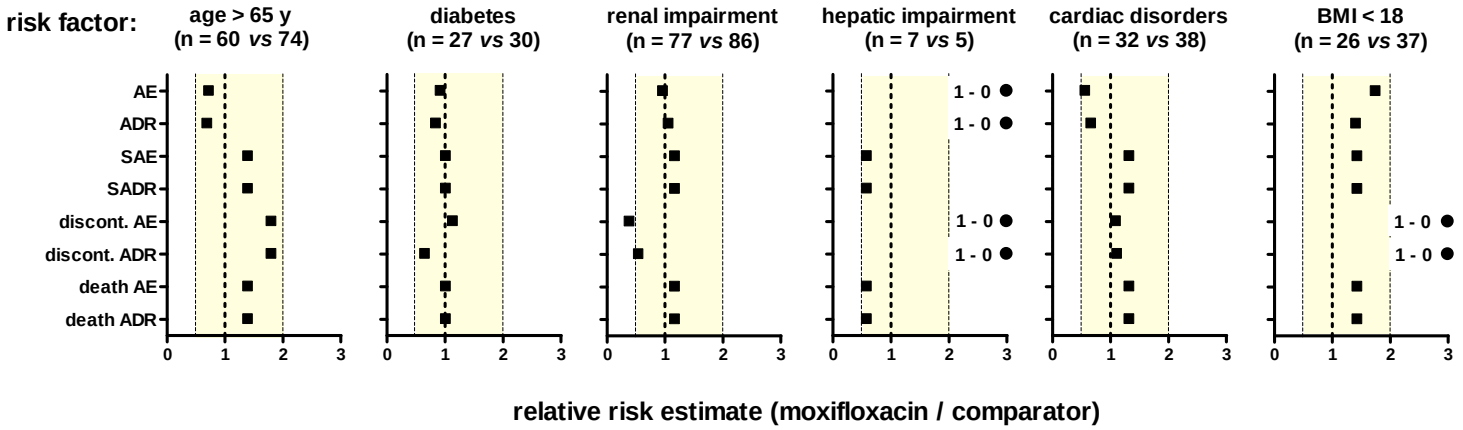
And what if we compare drugs ?

C. intravenous therapy

1. moxifloxacin *vs* β-lactam



2. moxifloxacin *vs* another fluroquinolone

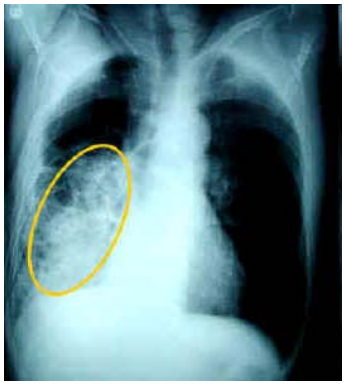


Conclusions (at this point)

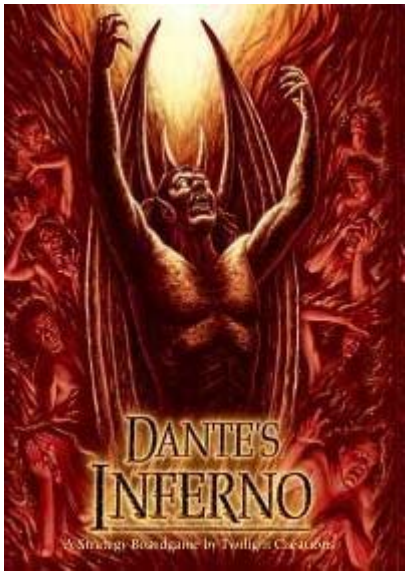
- The overall safety profile of moxifloxacin is similar to that of comparators from clinical trials
- More specifically, and with regard to recent questions:
  - Hepatic events reactions were very low and not superior in a statistically significant manner to comparators even if considering patients with 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

But what is "risk" ?

→ side effects ?



→ therapeutic failure ?

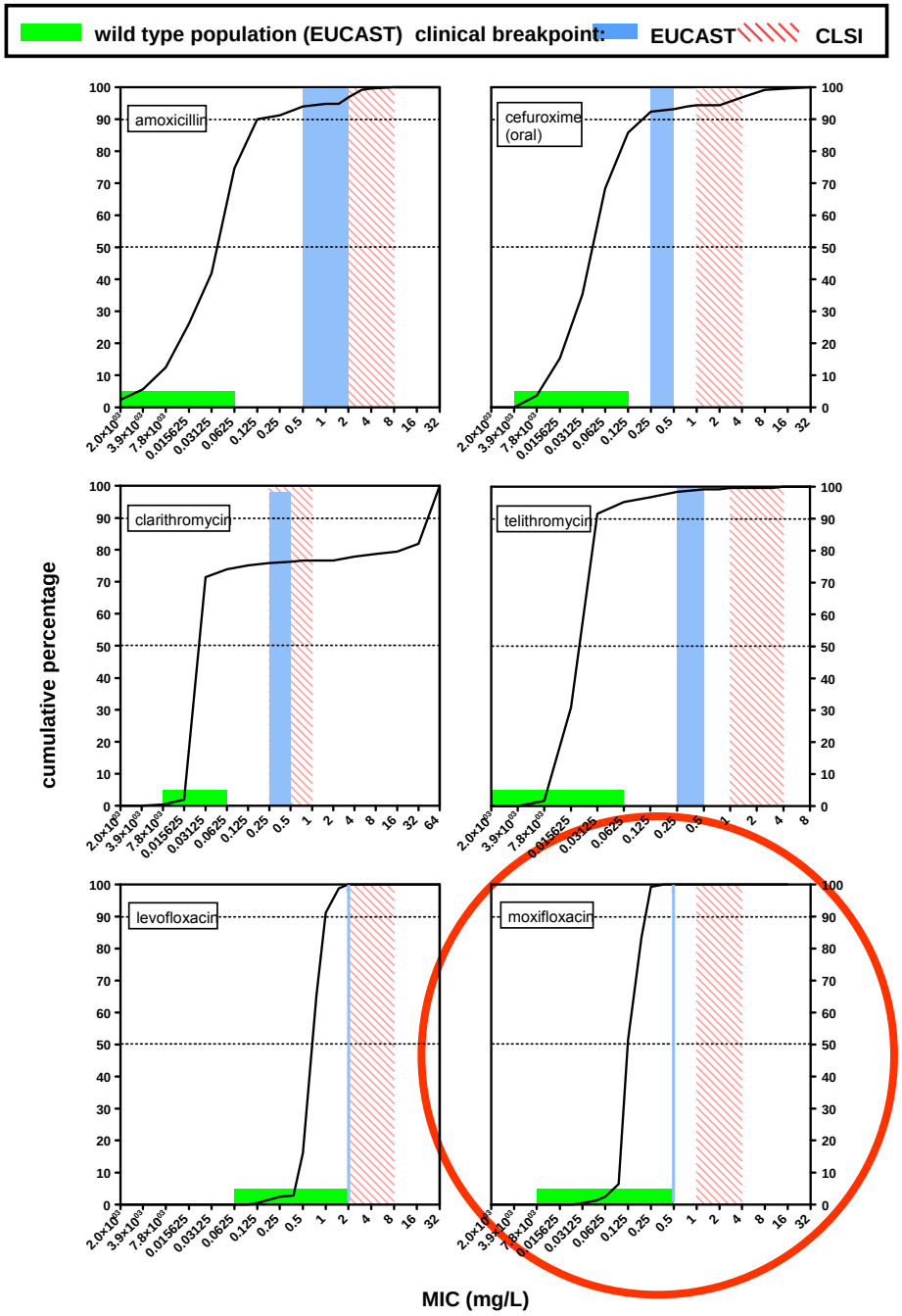


Is moxifloxacin still effective ?

International Journal of Antimicrobial Agents
IJAA-D-11-00658 – *In press*

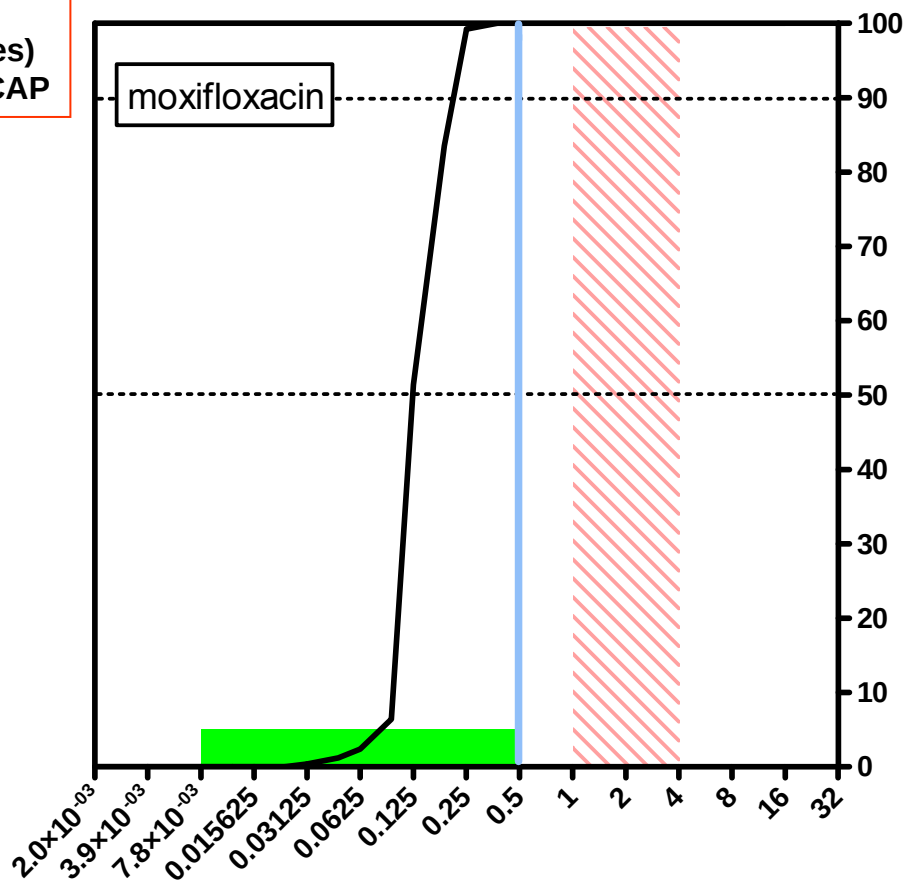
Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically-confirmed diagnosis of community-acquired pneumonia (CAP) in Belgium

Ann Lismond [a], Sylviane Carbonnelle [a, 1], Jan Verhaegen [b], Patricia Schatt [c], Annelies De Bel [d], Paul Jordens [e], Frédérique Jacobs [f], Anne Dediste [g], Frank Verschuren [h], Daniel Huang [i, 2], Paul M. Tulkens [a, *], Youri Glupczynski [j], Françoise Van Bambeke [a]



Is moxifloxacin still effective ?

S. pneumoniae
N= 249 (non-duplicates)
clinically-confirmed CAP

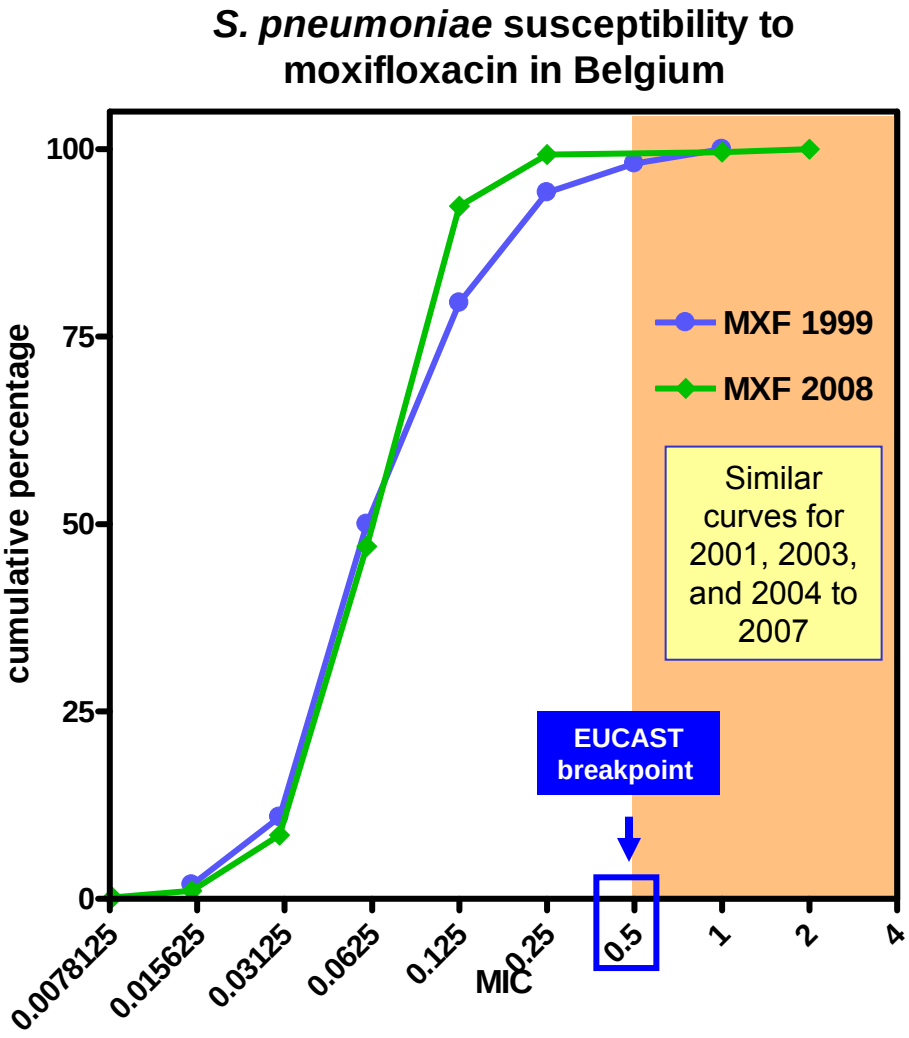


International Journal of Antimicrobi
IJAA-D-11-00658 – *In press*

Antimicrobial susceptibility of *Strep*
vaccinated and non-vaccinated pati
of community-acquired pneumonia

Ann Lismond [a], Sylviane Carbonnelle
Annelies De Bel [d], Paul Jordens [e], Fré
Verschuren [h], Daniel Huang [i, 2], Paul
Van Bambeke [a]

Moxifloxacin MIC's against *S. pneumoniae* have not increased in Belgium from 1999 to 2008



Facts:

From data of a <u>national</u> collection * independent from our own collection (shown on the previous slide)

- No change (and even improvement) in *S. pneumoniae* susceptibility to moxifloxacin from 1999 (pre-commercialization) to 2008 (7 years after launching **)
- in 2008, 99.3 % isolates were still below the EUCAST breakpoint (0.5 mg/L) **and at MIC values > 10-fold lower than the $C_{max.}$**

* Non invasive respiratory tract infections
** 1st respiratory quinolone in BE

Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 448 in 2008)
http://www.iph. fgov.be
Data available yearly for 1999 through 2008.
Presented at 19th ECCMID, May 2009, Helsinki, Finland (Vanhoof et al.)

Conclusions (Altogether)

- Moxifloxacin has kept over years an excellent activity against *S. pneumoniae* (and wil be effective against *S. aureus* up to an MIC of 0.125-1 mg/L) and should, therefore stand a as a useful alternative when so-called "*1st line antibiotics*" (for CAP, COPD or skin infections) have "stopped to work"

- The safety profile of moxifloxacin at 400 mg/day remains excellent with no statistically or medically significant difference with comparators (used often at a lower dose than recommended today)
- Thus, and based on all available evidence, the use of moxifloxacin should not be vitiated by excessive toxicity if it is prescribed for the correct indications and with due attention to the contraindications and warnings mentioned in the labeling

(Van Bambeke & Tulkens, Drug Saf. 2009;32(5):359-78
Tulkens et al. in preparation)

Flämischer Maler Hieronymus Bosch (c1450-1516) zeigt großer Fantasie in seinem Triptychon Altarpiece „das letzte Urteil“ (c1510-15, Akademie, Wien)

"Was auch als
Wahrheit oder Fabel
In tausend Büchern
dir erscheint,
Das alles ist ein Turm
zu Babel,
Wenn es die Liebe
nicht vereint."

J.W. von Goethe

Disclosures

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- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics
- the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:

- all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site *
- P.M. Tulkens is member of the Committee organising public campaigns for appropriate use of antibiotics in Belgium since 2000 **

* http://www.facm.ucl.ac.be/publicat_facm.htm
** http://www.antibiotiques.org/

Selected publications in relation to this presentation:

- Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf. 2009;32(5):359-78. PubMed PMID: 19419232.
- Van Bambeke F, Reinert RR, Appelbaum PC, Tulkens PM, Peetermans WE. Multidrug-resistant Streptococcus pneumoniae infections: current and future therapeutic options. Drugs. 2007;67(16):2355-82. Review. PubMed PMID: 17983256.
- Lismond et al. Antimicrobial susceptibility of Streptococcus pneumoniae isolates from vaccinated and non-vaccinated patients with a clinically-confirmed diagnosis of community-acquired pneumonia (CAP) in Belgium. Intern. J. Antimicrob. Agents, 2001, *in press*