



Antibiotiques et Cardiotoxicité

Pascal Voiriot (Nancy) – 11.10.2005

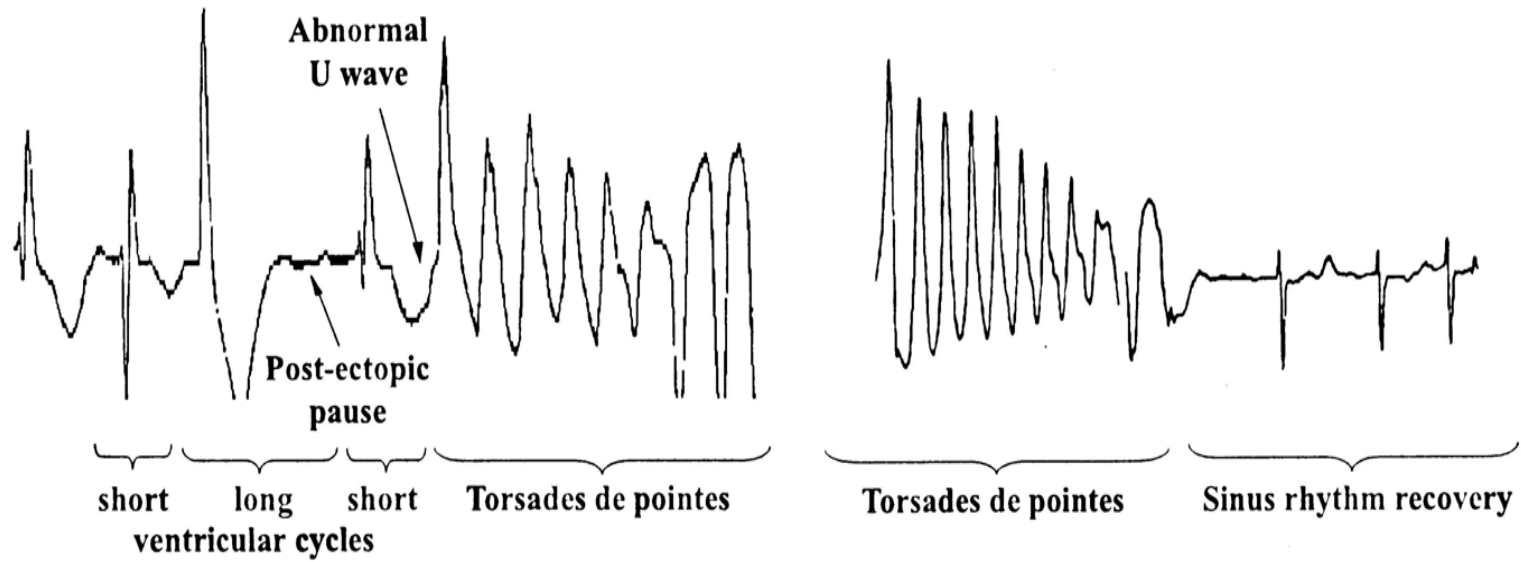
Background : Drug, QT prolongation & Withdrawal

- The single most common cause of the **withdrawal** (or restriction of the use) of drugs, in the past decade, the prolongation of the **QT interval associated** with polymorphic ventricular tachycardia or **Torsade de Pointes** ...
- For this reason, along this decade, **9 structurally unrelated** « **non cardiovascular drugs** » have been removed from the market or severely restricted :

- Terfenadine
- Astemizole
- **Grepafloxacin**
- Torodiline

- Droperidol
- Lidoflazine
- Sertindole
- Levomethadyl
- Cisapride

Torsade de Pointe



Background : Terfenadine « story »

- The « index » drug for the problem is **terfenadine**.
 - This drug was the **first non-sedating antihistamine** and was wildly popular in the treatment of allergic rhinitis.
 - **Several years after** its introduction, reports of syncope, polymorphic ventricular tachycardia (TdP) and sudden cardiac death began to appear, especially **with concomitant use of antibiotics**.

- By the mid 1990s, the increasing number of fatal cases lead to regulatory concern with :
 - 1° extensive labeling restrictions,
 - 2° drug withdrawal



Drugs that can prolong the QT interval

<i>Class reported</i>	<i>Drug</i>	<i>TdP reported</i>
Anti-arrhythmic drugs	Ajmaline	+
	Almokalant	+
	Amiodarone	+
	Aprinidine	+
	Azimilide	+
	Bretylum	+
	clofilium	+
	Dofetilide	+
	Disopyramide	+
	Ibutilide	+
	N-acetyl-procainamide	+
	Procainamide	+
	Propafenone	+
	Quinidine	+
	Sematilide	+
	D,L-sotalol, D,-sotalol	+
Vasodilators/anti-ischemic agents	Bepidil	+
	Lidoflazine	+
	Prenylamine	+
	Papaverine (intracoronary)	+

adapted from : W Haverkamp et al. / Cardiovascular Research 47 (2000) 219-233

Drugs that can prolong the QT interval

<i>Class reported</i>	<i>Drug</i>	<i>TdP reported</i>
Psychiatric drugs	Amitriptyline	+
	Clonipramine	
	Cloral hydrate	+
	Chlorpromazine	+
	Citalopram	+
	Desipramine	+
	Doxepin	+
	Droperidol	+
	Fluphenazine	
	Haloperidol	+
	Imipramine	+
	Lithium	+
	Maprotiline	+
	Mesoridazine	
	Nortriptyline	
	Pericycline	
	Pimozide	
	Prochlorperazine	
	Sertindole	+
	Sultopride	+
	Thioridazine	+
	Timiperone	+
Trifluoperazine		
Zimeldine	+	

adapted from : W Haverkamp et al. / Cardiovascular Research 47 (2000) 219-233

Drugs that can prolong the QT interval

Class	Drug	TdP reported
Anti-histaminics	Astemizole	+
	Diphenhydramine	+
	Ebastine	
	Hydroxyzine	
	Terfenadine	+
Miscellaneous drugs	Budipine	+
	Cisapride	+
	Probucol	+
	Terodiline	+
	Vasopressine	+

adapted from : W Haverkamp et al. / Cardiovascular Research 47 (2000) 219-233

Drugs that can prolong the QT interval

<i>Class reported</i>	<i>Drug</i>	<i>TdP reported</i>
Antimicrobial and antimalarial drugs	Amantadine	+
	Clarythromycin	+
	Chloroquine	+
	Cotrimoxazole	+
	Erythromycin	+
	Grepafloxacin	+
	Halofantrine	+
	Ketoconazole	+
	Pentamidine	+
	Quinine	+
	Spiramycine	+
Sparfloxacin	+	

adapted from : W Haverkamp et al. / Cardiovascular Research 47 (2000) 219-233

Background : What is the « concern » ?

- Prolonged QT *versus* Torsade de Pointes ???
 - QT prolongation **per se** is not a serious event.
 - The **adverse event of concern** is TdP or VT
 - For quinidine,
 - TdP : 1:4000
 - Major QT prolongation : 1:20
 - As an extrapolation, we can assume that TdP occurrence is about 1/200 (0.5%) of major QT prolongation
 - For non cardiovascular drugs, the occurrence is much lower
 - The background incidence for TdP in the general population has been reported to be 8.6 cases per 10 million people.
 - The incidence for the population receiving any drug therapy is estimated to be 40 cases per 10 million people (**x4**)

QT prolongation : a « surrogate » for TdP

- For non-cardiac drugs, the TdP and sudden death frequencies are very low.
Therefore, TdP was usually not detected in clinical trials of non-cardiac drugs and the sudden death liability became manifest only during post-marketing surveillance.
- Faced with this dilemma, agencies have resorted to the use of QT prolongation as a surrogate for TdP, with the following values to consider.

From : Moss A.J. -Am J Cardiol 1993, 72: 23B-25B

QTc	Adult Males	Adult Females
Normal	≤430 msec	≤450 msec
Borderline	431-450 msec	451-470 msec
Prolonged	>450 msec	>470 msec

delta QTc/baseline :

From : EMEA-CPMP : Point to consider ... 1996
ICH E14 final document – May 2005

Normal	≤30 msec
Borderline	31-60 msec
Prolonged	>60 msec



from Brown A W. – Cell Calcium - 2004; 35 : 543–547



Rational for outlier definition

- In patients receiving sotalol, for a high-risk group of patients with clinically significant cardiac arrhythmias,
- those with a drug induced
 - *QTc >500 msec*
 - *or an increase in QTc of >65 msec*
- had a >3% incidence of TdP



How good is the QT prolongation surrogate ? Not very ...

- 1° QT interval varies with heart rate
- 2° Terfenadine and cisapride only showed an a slight average QT increase of about 10 ms
 - < 3% of the regular QT interval
 - within the daily variability of QT in an individual.
- 3° the relationship between QT prolongation and TdP is a weak power function and has no threshold to identify imminent danger
- 4° the definitive mechanism linking QT prolongation to TdP is still unknown
- 5° the relationship may be drug-dependent; for equivalent QT prolongation drugs may differ in the frequency of TdP (sotalol *versus* dofetilide; amiodarone *versus* almokalant)

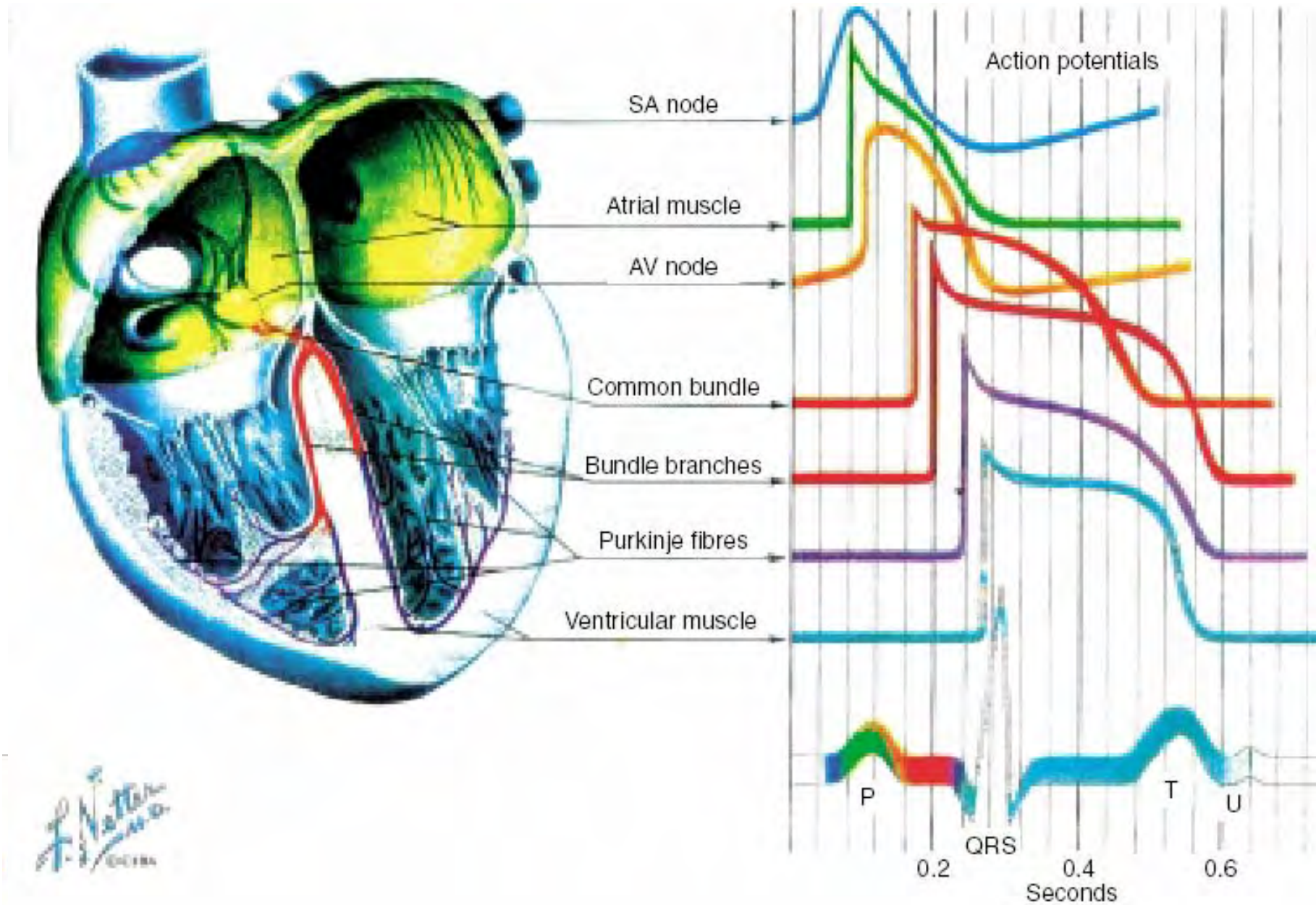
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

DRAFT CONSENSUS GUIDELINE

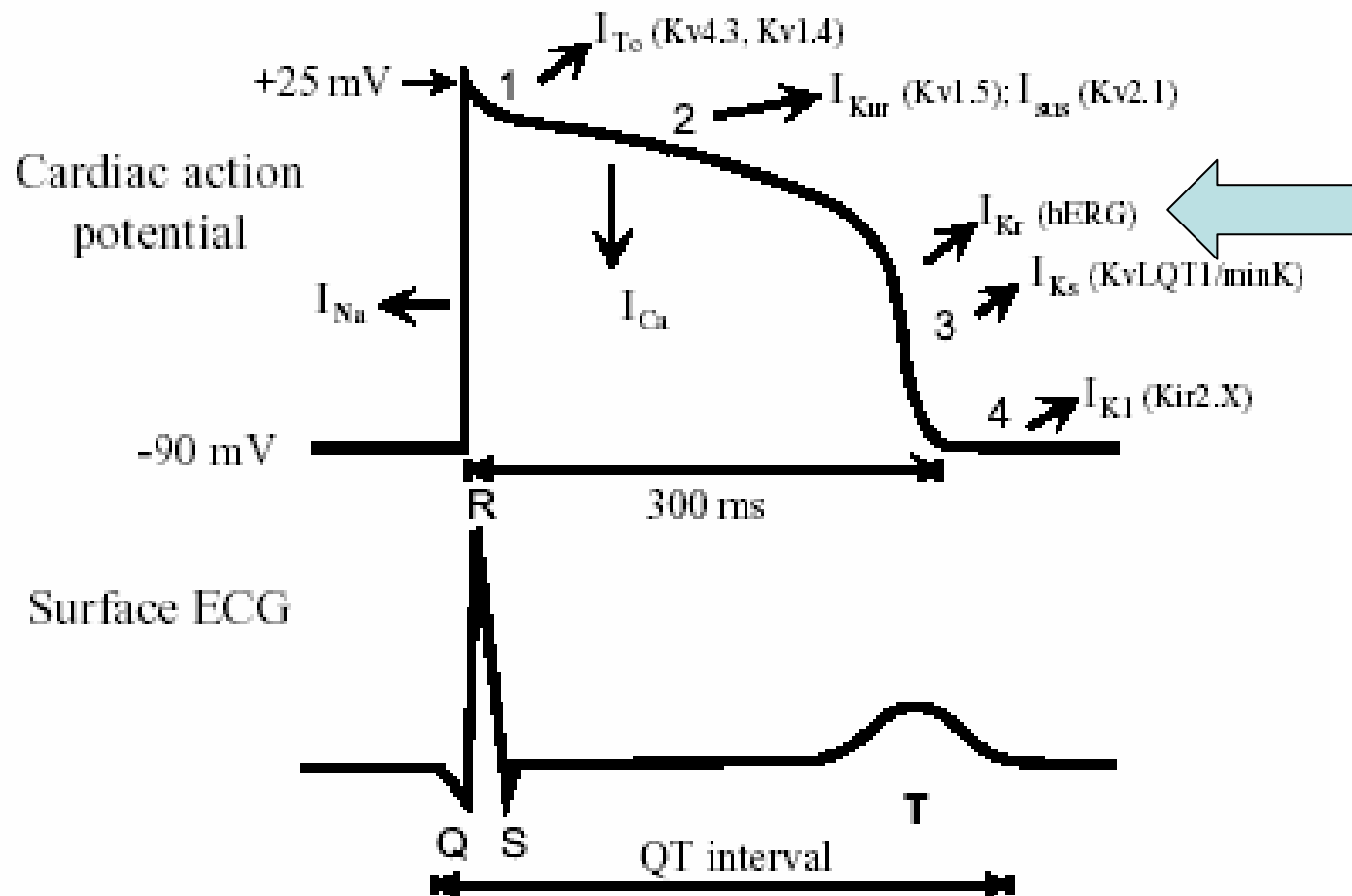
**SAFETY PHARMACOLOGY STUDIES FOR ASSESSING THE
POTENTIAL FOR DELAYED VENTRICULAR
REPOLARIZATION
(QT INTERVAL PROLONGATION)
BY HUMAN PHARMACEUTICALS**

- Three complementary methods :
 - IKr channel blockage assessment : Molecular study (HERG)
 - A.P prolongation assessment : Cellular study (Pukinje fibers)
 - In vivo study : rodent

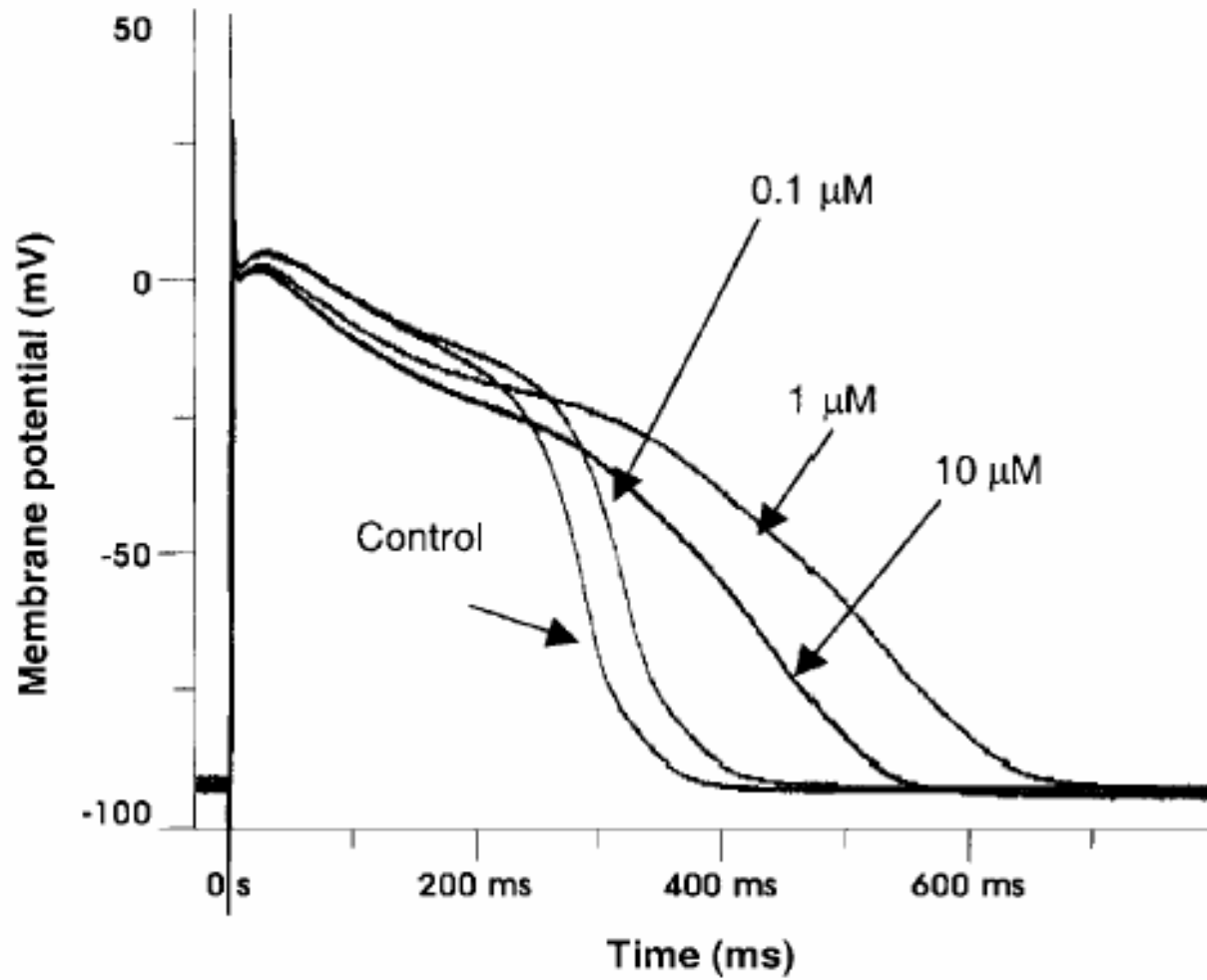
- Inter-agency discrepancies (FDA, EMEA, Japan)



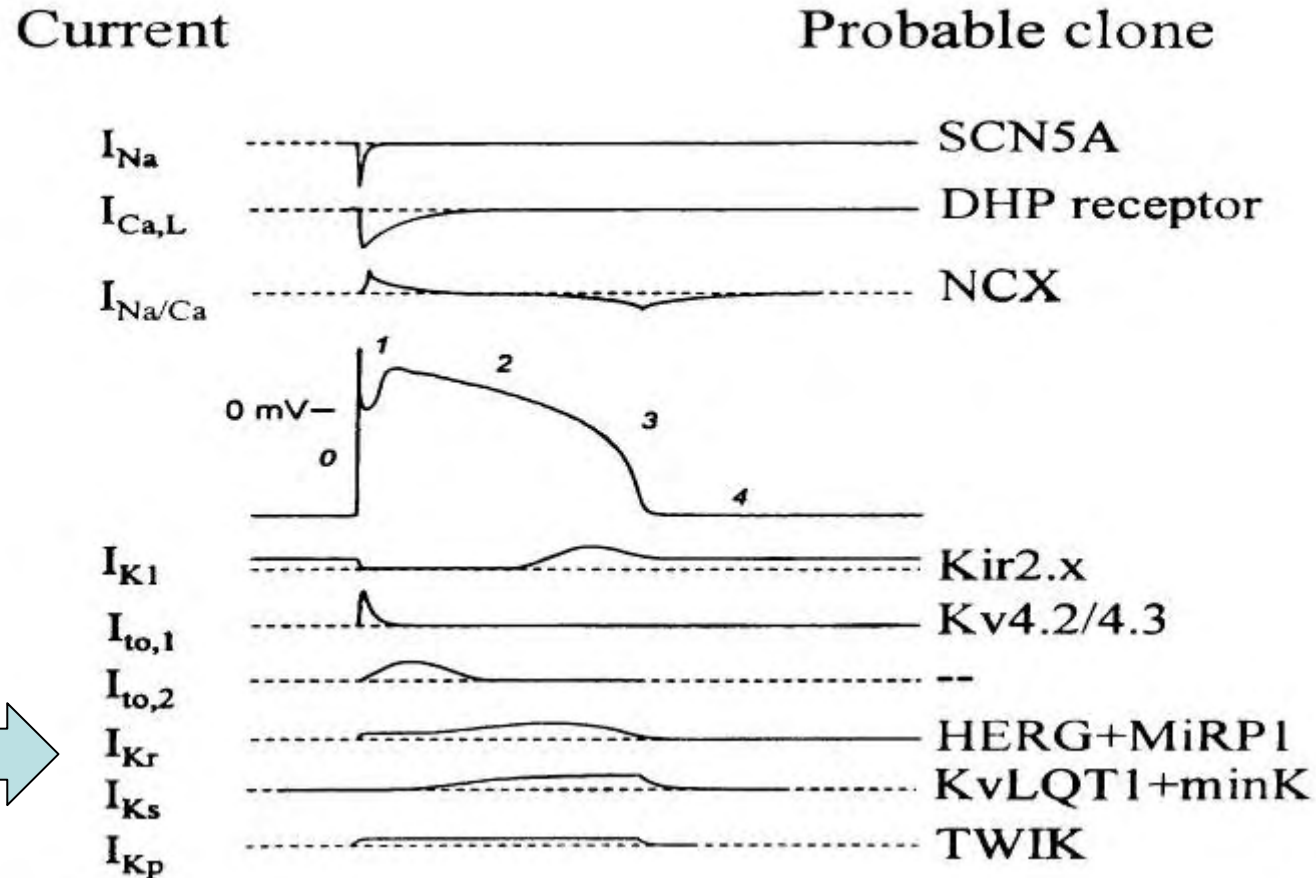
Relationship between cardiac membrane currents, action potential duration and the QT interval of the ECG



Biphasic effect of cisapride on dog Purkinje fiber AP

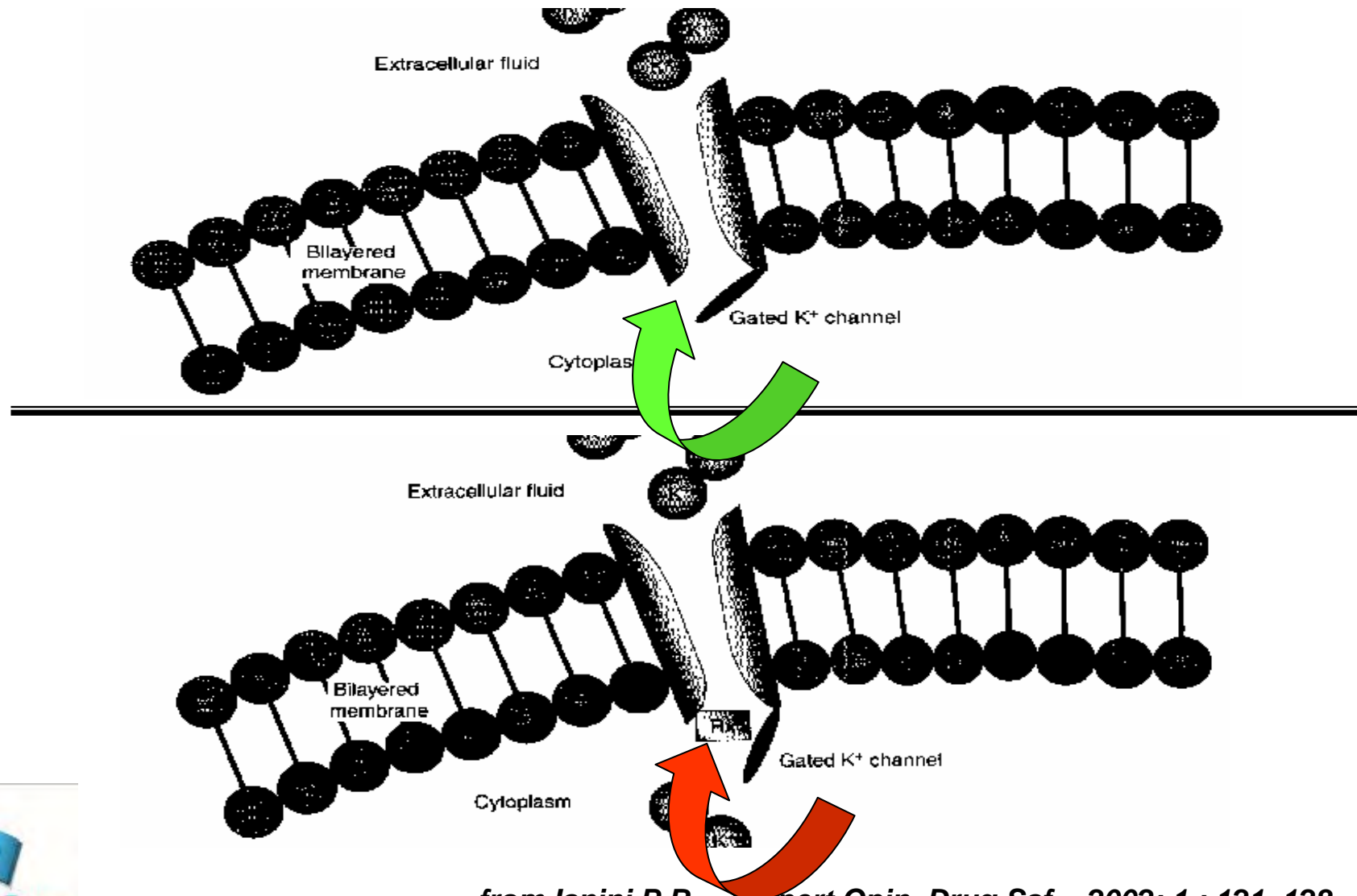


Ionic and molecular basis of the cardiac action potential

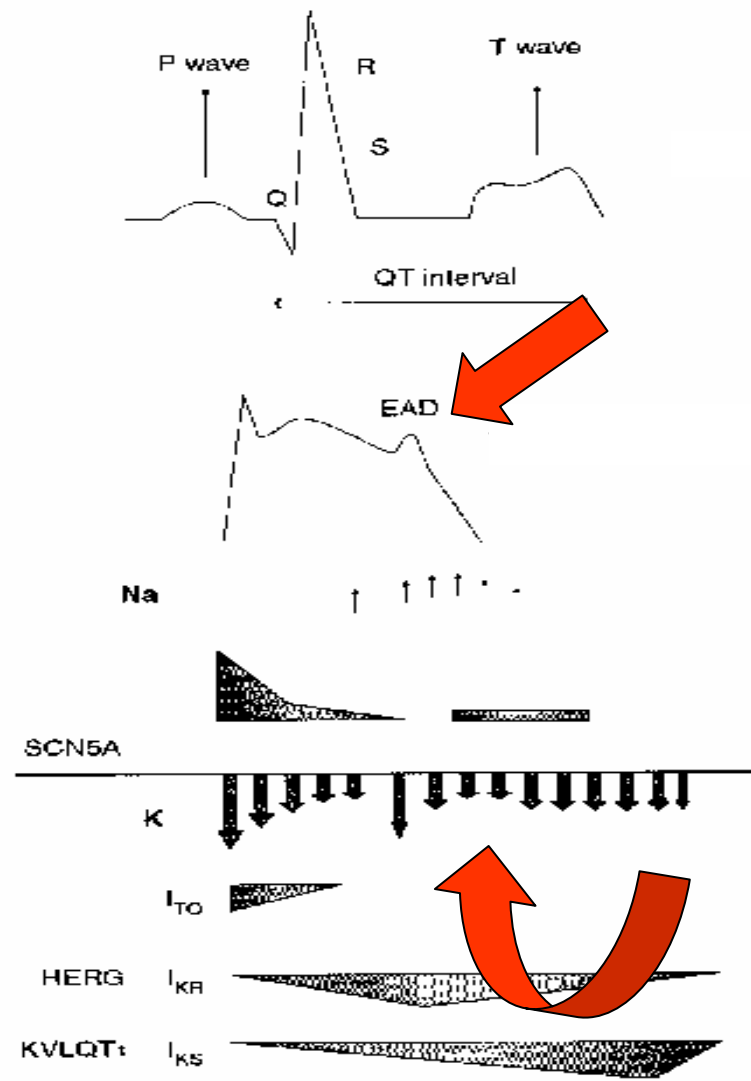
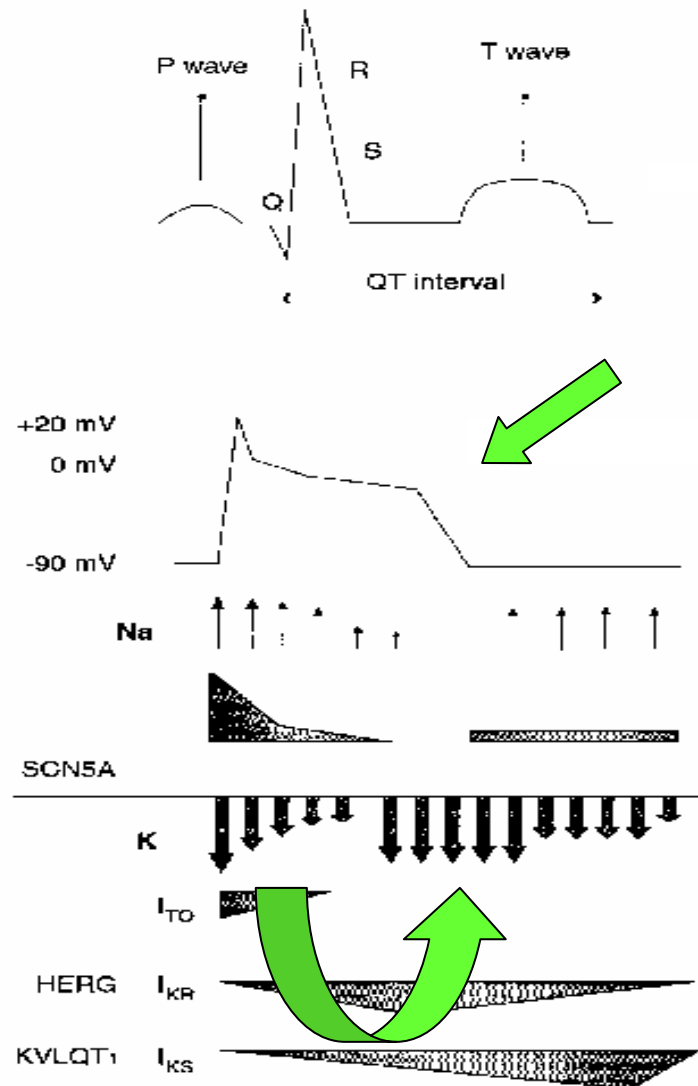


The waveform results from multiple, successively activating depolarizing inward currents (*downward*) and repolarizing outward currents (*upward*). The established or most probable clones are indicated. Numbers denote the phase of the action potential

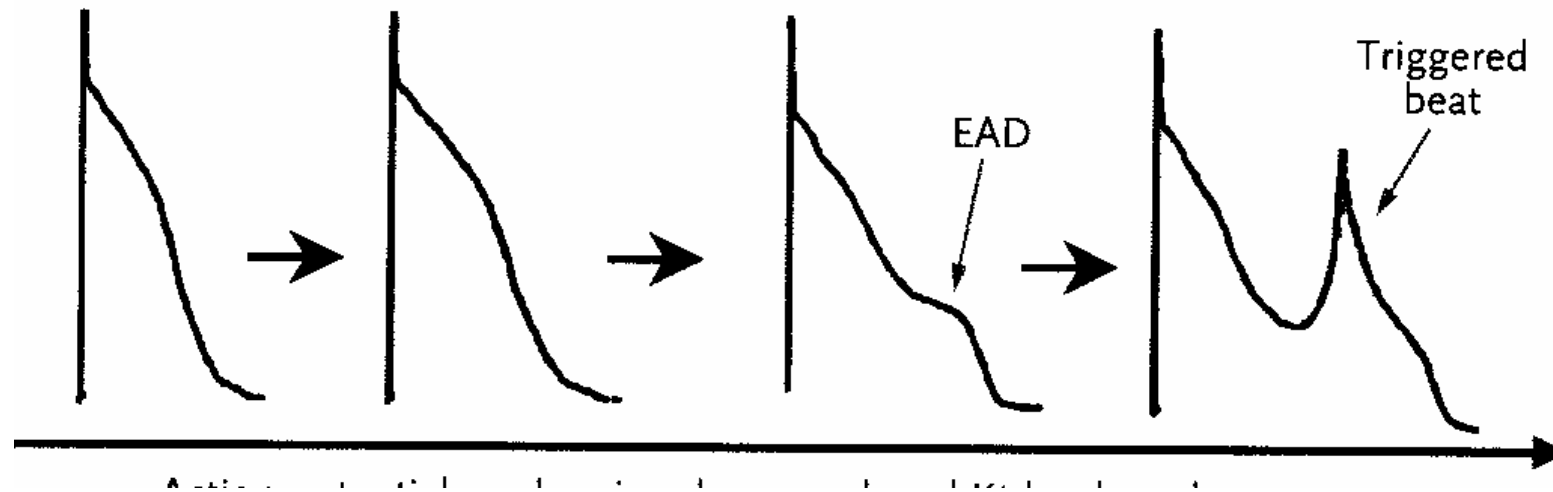
Cardiac myocytes membrane repolarisation via HERG potassium channel

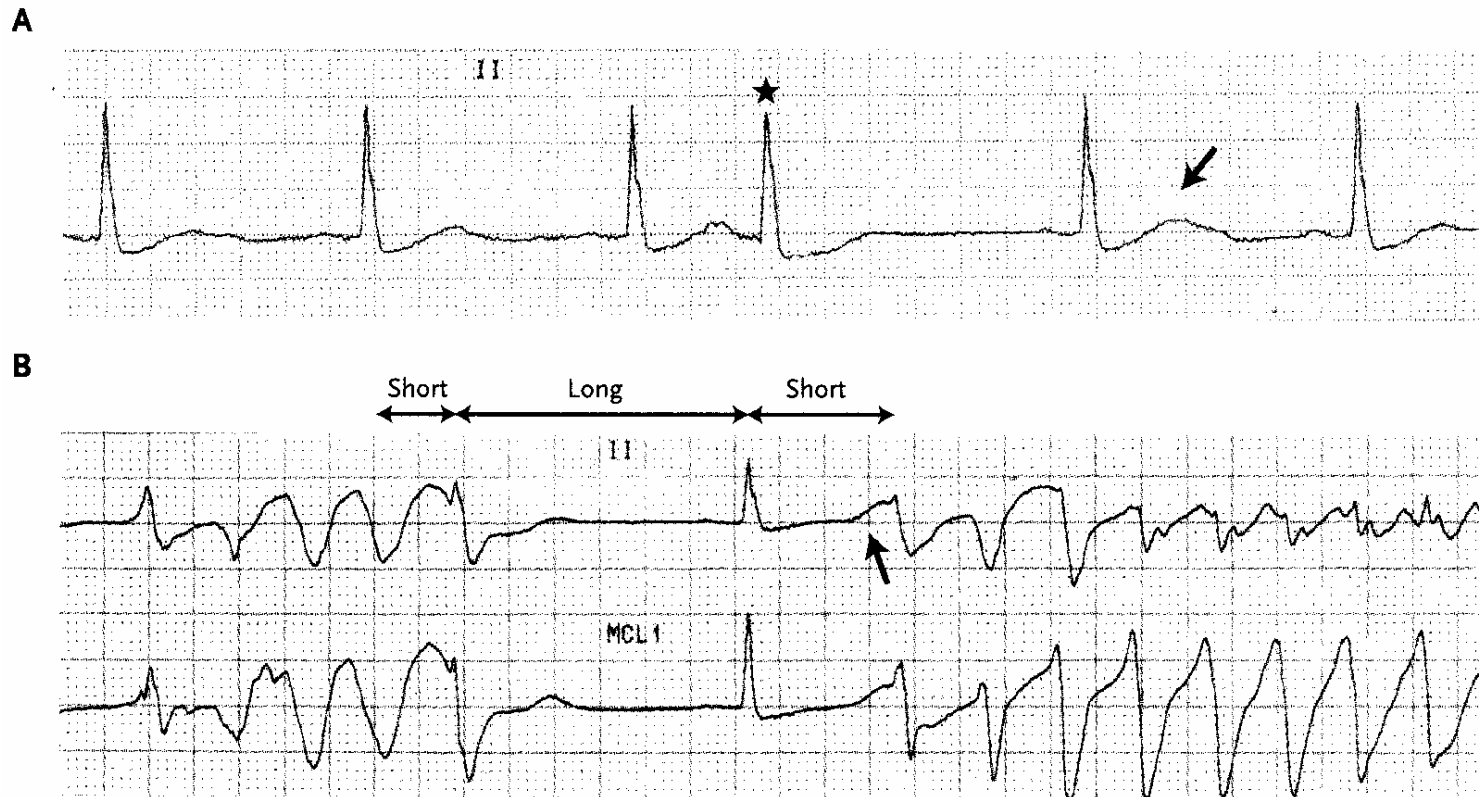


Relationship of surface ECG, myocyte electrogram & ion flux with blockage of HERG channel



Basic mechanisms in arrhythmia related to long QT interval





Quelque repères précliniques pour le clinicien

■ HERG studies

□ IC_{50}

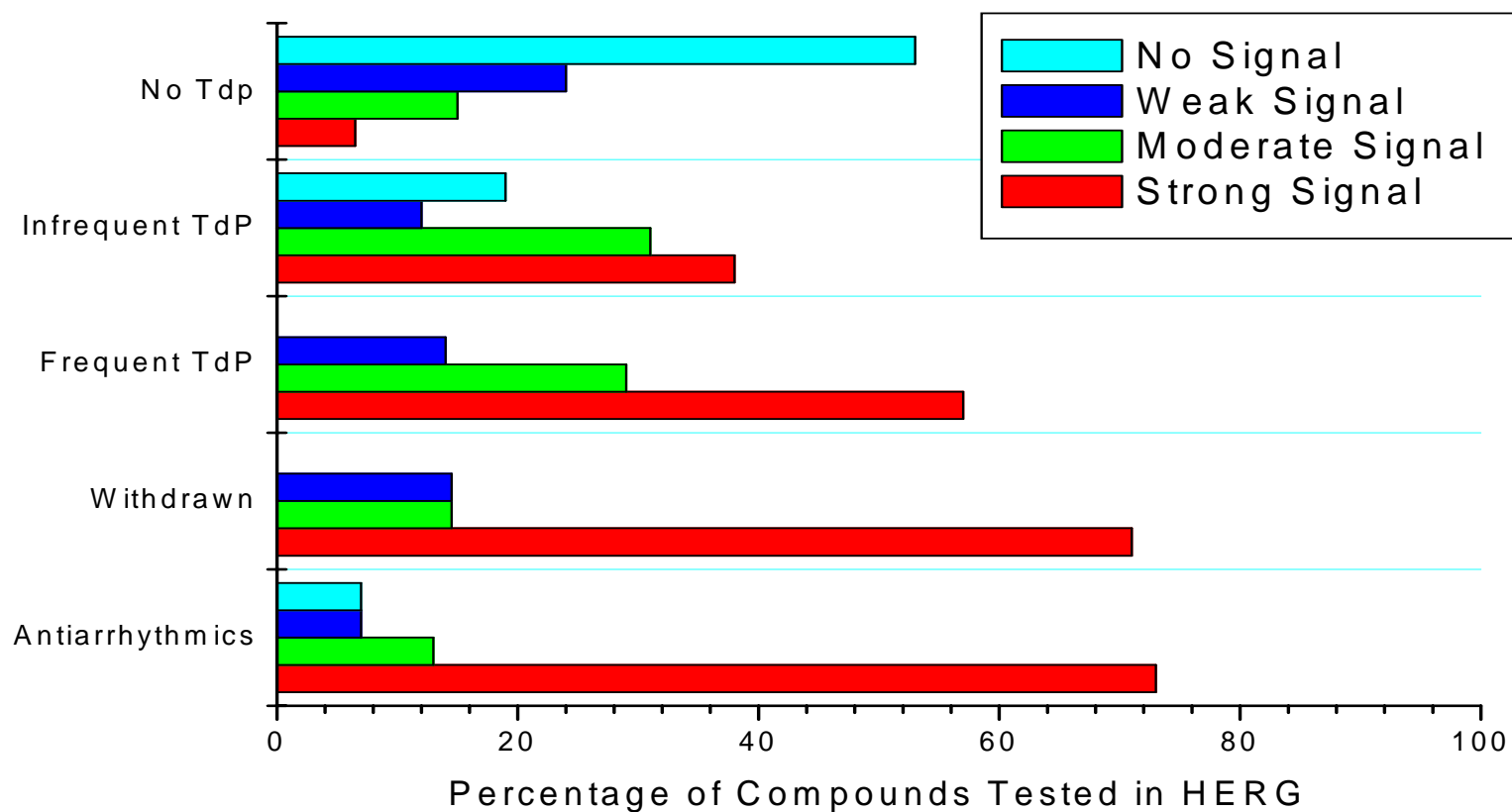
- $<1\mu M = >0$
- $>10\mu M = <0$

□ Safety Margin (S.M.)

- $IC_{50} / C_{max_{free}} >30 \text{ to } 100 = <0$
- $IC_{50} / C_{max_{free}} <10 = >0$

hERG/IKr PREDICTIVE VALUES of TdP

→ data alone is a remarkably good predictor of QT risk”





The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 17 December 1997
CPMP/986/96

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**POINTS TO CONSIDER:
THE ASSESSMENT OF THE POTENTIAL FOR QT INTERVAL
PROLONGATION BY
NON-CARDIOVASCULAR MEDICINAL PRODUCTS**

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

DRAFT CONSENSUS GUIDELINE

**THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION
AND PROARRHYTHMIC POTENTIAL
FOR NON-ANTIARRHYTHMIC DRUGS
E14**

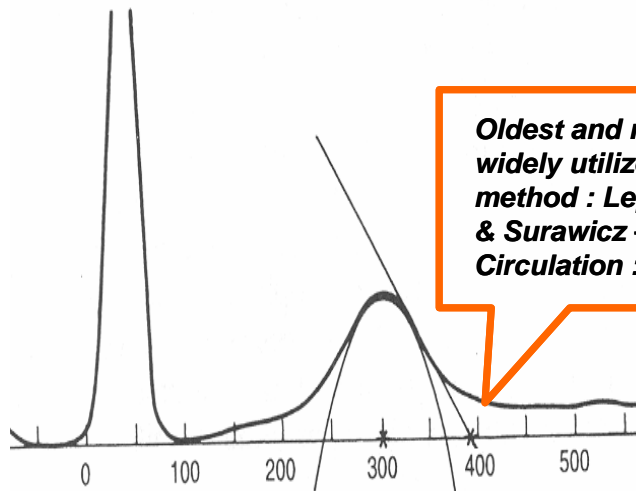
Released for Consultation
at *Step 2* of the ICH Process
on 10 June 2004
by the ICH Steering Committee

QT interval Measurements: End of QT Interval

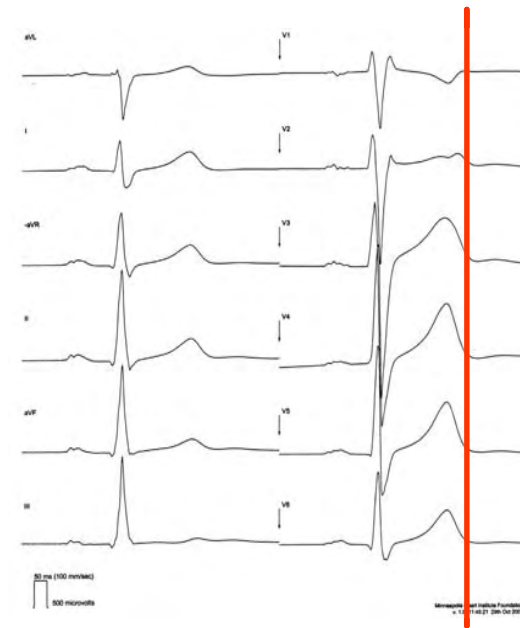
■ **Tangent** & intersect with baseline

OR

■ **Vertical Calipers** ???



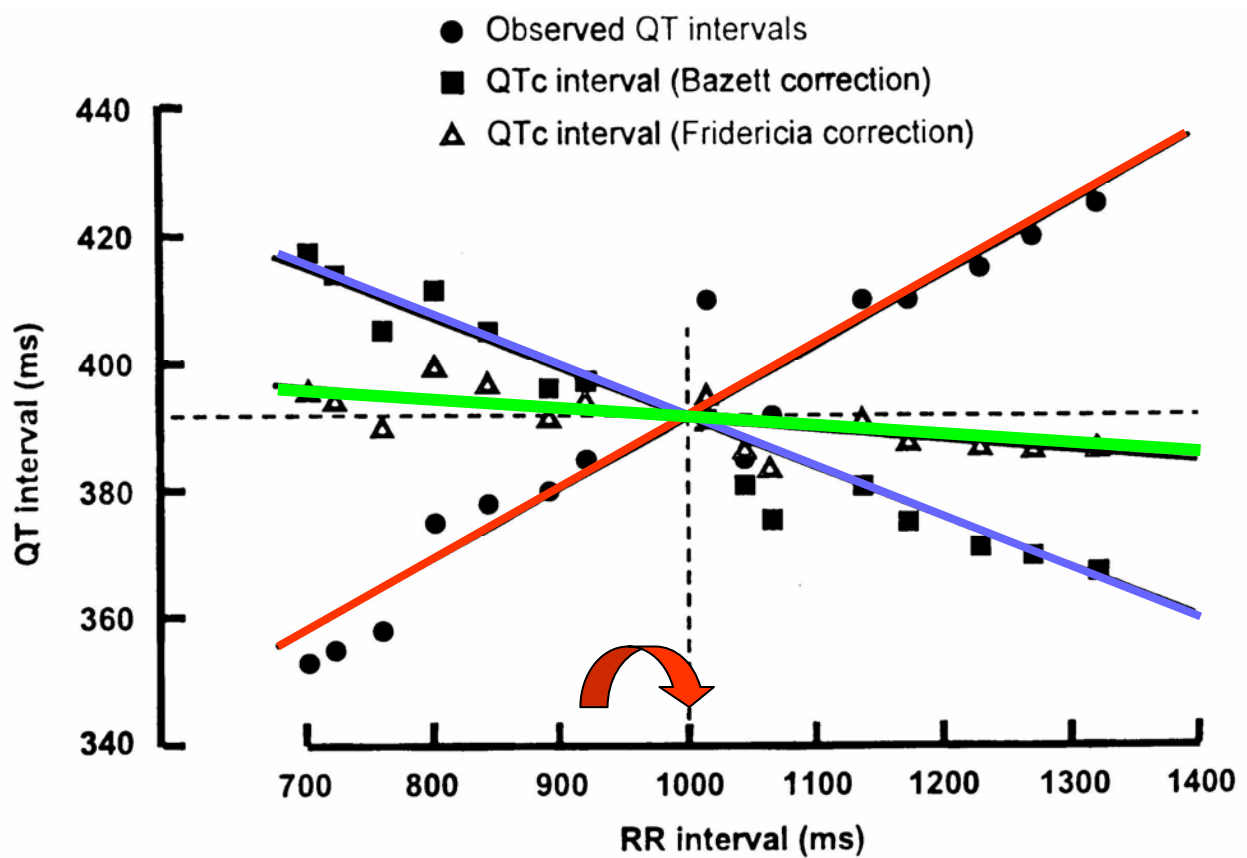
Oldest and more widely utilized method : Lepeshkin & Surawicz – Circulation : 1952



Adapted from : E.H. Locati - in : *Non Invasive Electrocardiography in Clinical Practice 2001* , p80 – Futura

Adapted from D. Mortara- 2003

QT Interval Measurements: QT correction for Heart Rate



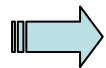
Adapted from : Caverio - *Exp. Opin. Pharmacother.* 2000, 1: 1-27

QT Interval Measurements: QT correction for Heart Rate



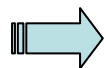
Formulas of the generic form $QT_c = QT/RR^\alpha$

Mayeda	$\alpha = 0.604$
Bazett	$\alpha = 0.5$
Boudolas et al.	$\alpha = 0.398$
Fridericia	$\alpha = 0.333$
Yoshinaga et al.	$\alpha = 0.31$
Kawataki et al.	$\alpha = 0.25$



Formulas of the generic form $QT_c = QT + \beta \times (1.0 - RR)$

Sagie et al. (Framingham)	$\beta = 0.154$
Ljung	$\beta = 0.200$
Schlamowitz	$\beta = 0.205$



Formulas of the generic form $QT_c = QT + \beta/1000 \times (HR - 60)$

Rickards et al.	$\beta = 1.87$
Hodges et al.	$\beta = 1.75$
Klingfield et al.	$\beta = 1.32$
Wohlfart and Pahlm	$\beta = 1.23$

QT Interval Measurements: QT correction for Heart Rate



Formula in the form $QT_c = QT + \Phi(HR)$

Karjalainen et al.

Φ in a published table



Formula in the form $QT_c = QT / \log_{10}(RR + \varepsilon)$

Ashman

$\varepsilon = 0.07$



Formula in the form $QT_c = QT - \delta + \delta/RR$

Kovacs

$\delta = 0.12$



Formula in the form $QT_c = QT - \delta / (1 + \xi \times HR) + \beta$

Rautaharju et al.

$\delta = 0.656, \xi = 0.01, \beta = 0.41$



Formula in the form $QT_c = QT + \beta - \xi \times e^{(\chi \times HR)}$

Arrowood et al.

$\beta = 0.304, \xi = 0.492, \chi = -0.008$



Formulas in the generic form $QT_c = QT + \beta - \xi \times e^{(\chi \times RR)}$

Sarma et al.

$\beta = -0.0149, \xi = 0.664, \chi = -2.7$

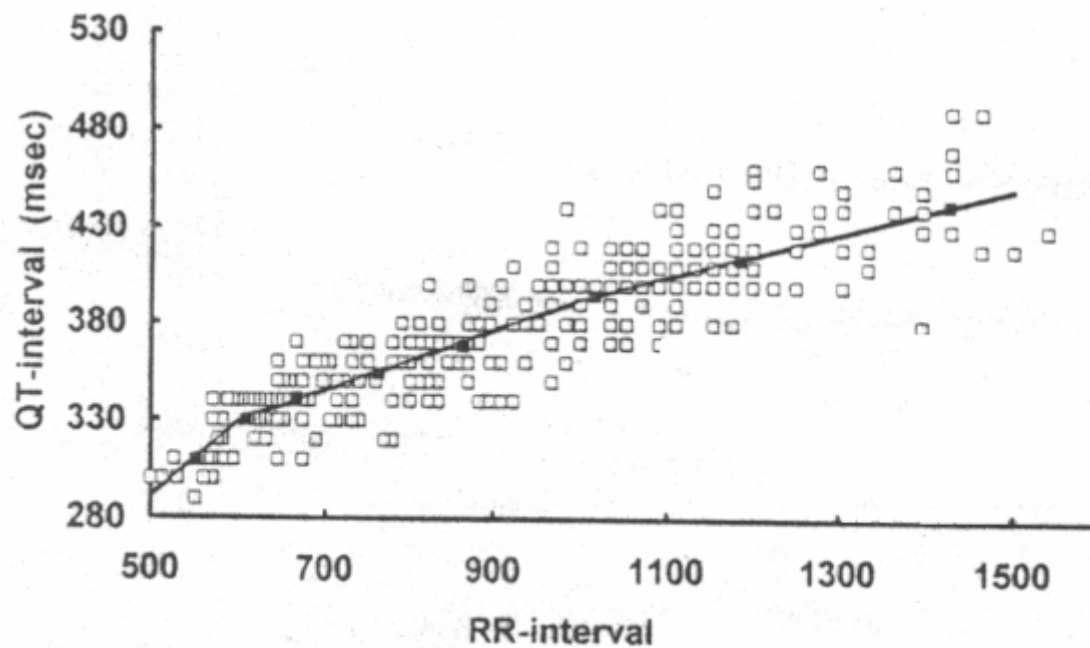
Lecocq et al.

$\beta = -0.017, \xi = 0.676, \chi = -3.7$

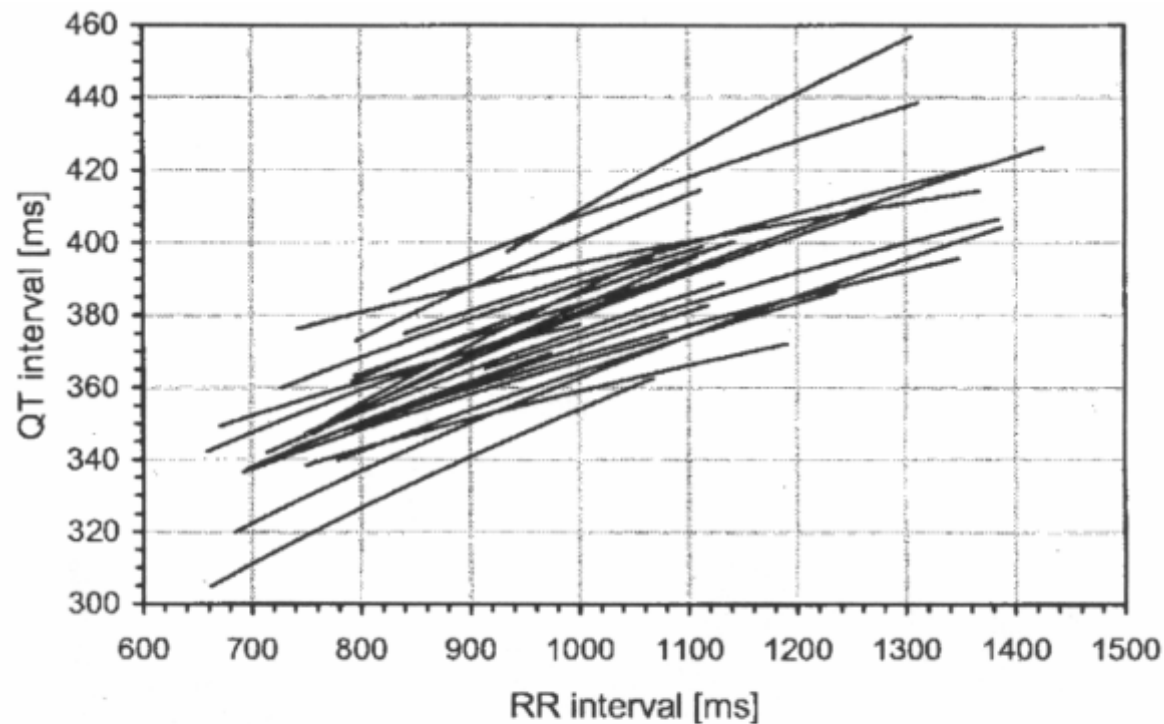


QT Interval Measurements: QT correction for Heart Rate

Relation between the QT and RR intervals in rest electrocardiograms of 324 young men. Equations for the regression line are as follows: RR interval <600 ms, $QT = 0.384RR + 99$; RR interval 600 to 1,000 ms, $QT = 0.156RR + 236$; and RR interval >1,000 ms, $QT = 0.116RR + 277$. **Open squares** = individual data points; **closed squares** = mean data points at heart rate subintervals of 10 beats/min.



QT Interval Measurements: QT correction for Heart Rate



Individual drug-free QT/RR regressions for individual subjects of the study. Each line corresponds to one subject and shows the optimum QT/RR nonlinear regression. The extent of each line corresponds to the range of the available drug-free RR interval data.

Risk factors for Torsade de Pointe

- Female sex¹⁰
- Hypokalemia^{11,12}
- Bradycardia^{11,12}
- Recent conversion from atrial fibrillation, especially with a QT-prolonging drug^{13,14}
- Congestive heart failure¹⁵
- Digitalis therapy¹⁶
- High drug concentrations (with the exception of quinidine)
- Rapid rate of intravenous infusion with a QT-prolonging drug¹⁷
- Base-line QT prolongation¹⁶
- Subclinical long-QT syndrome^{18,19}
- Ion-channel polymorphisms²⁰⁻²²
- Severe hypomagnesemia



Antimicrobial agents & TdP risk



Are the betalactamines at risk of QTprolongation/TdP ??

- **No report**
- **No clinical nor preclinical signal**
- **Could be considered as negative comparator for QT change studies involving other antibiotics « at risk »**



QT prolongation & TdP by Antimicrobial class

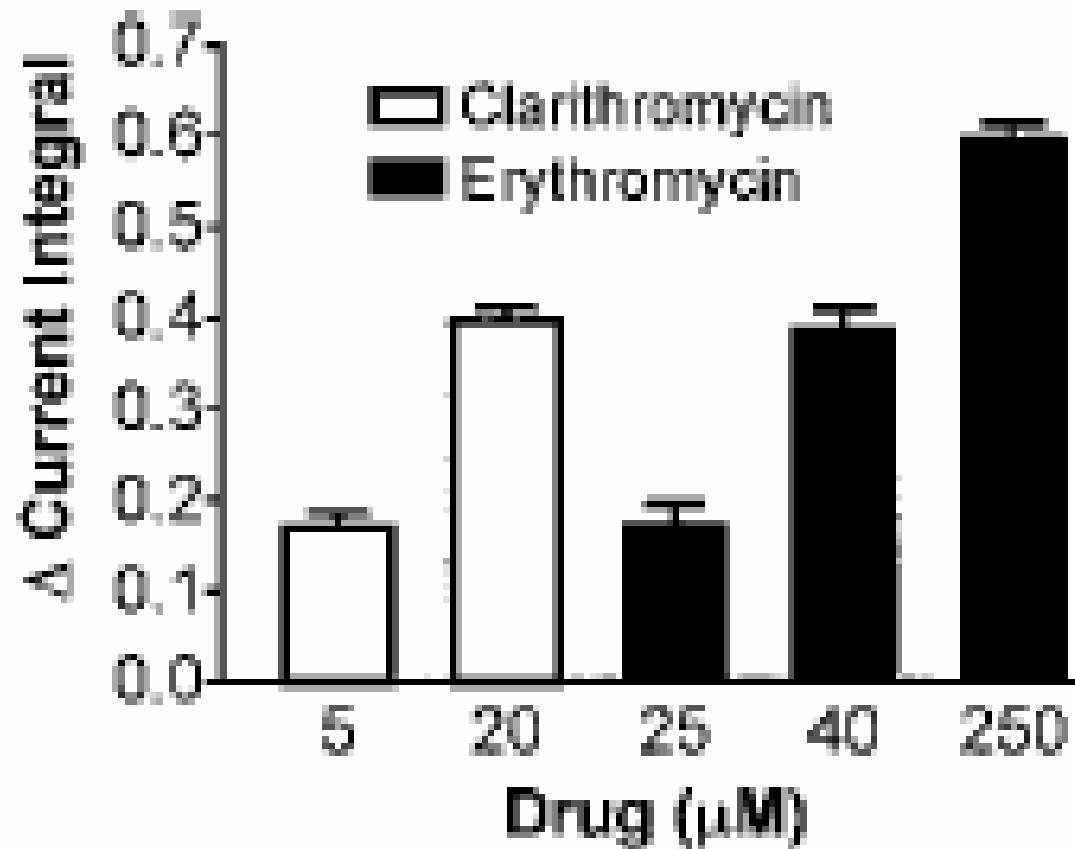
- Macrolides, azalides, ketolides
- Fluoroquinolones
- Azoles
- Miscellaneous
 - Cotrimoxazole
 - Pentamidine
 - Clindamycine



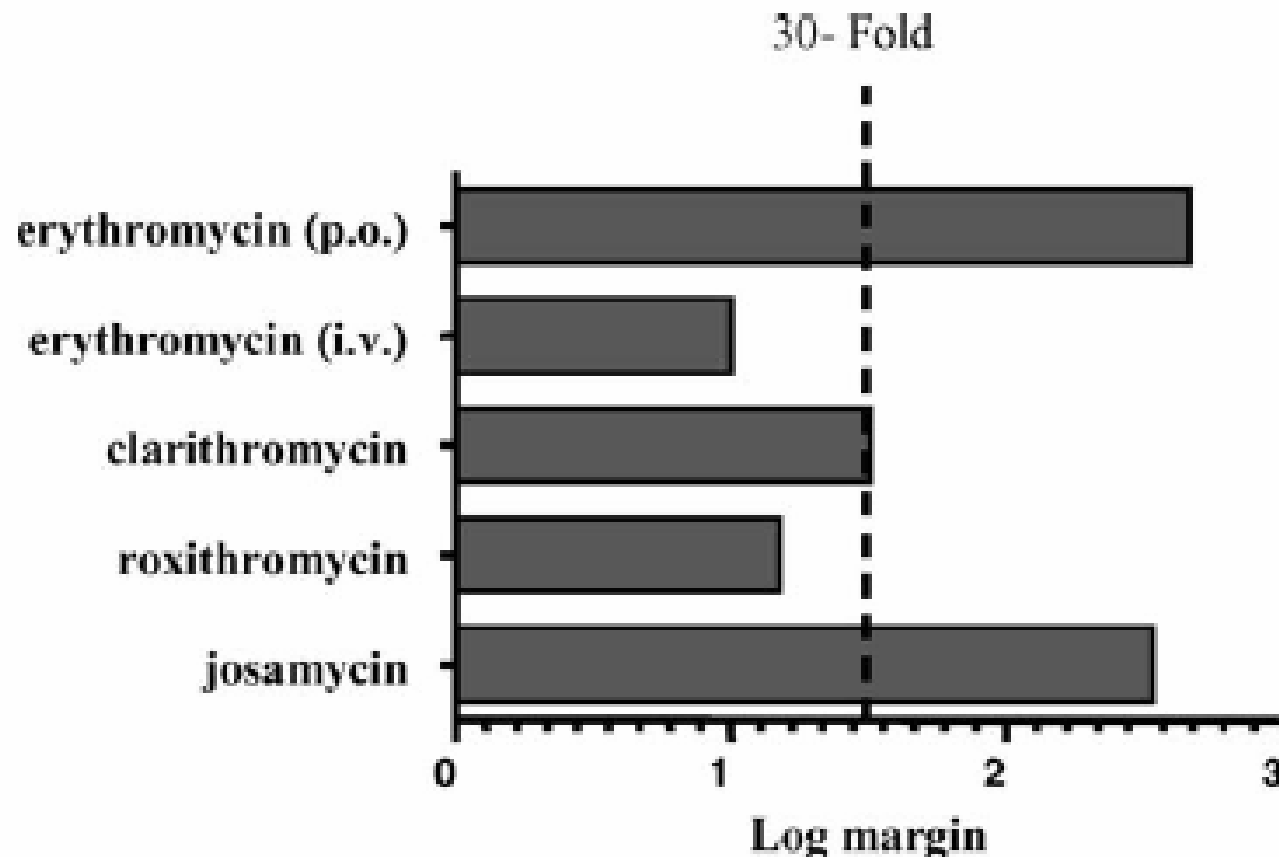
QT prolongation & TdP by Antimicrobial class

- **Macrolides, azalides, ketolides**
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Mean reductions in current integral for Clarithromycin & Erythromycin various concentrations



Margins of safety (expressed in log units) of antibacterial macrolides.



Values were obtained from IC50 values for inhibition of HERG K⁺ channels divided by the free C_{max} measured after oral administration. The vertical dotted line indicates a ratio of 30, which is considered an acceptable safety margin.

HERG blockade : inter-studies discrepancies

- The IC50 value for **clarithromycin** obtained in recent study (IC50 = 45.7 μ M) is more than **10 fold lower** than that reported in a previous one (IC50 = 0.75 mM).
- Difference in potency of clarithromycin block of HERG current observed in various studies probably is **methodological** (time and temperature dependance).
 - pulse durations (500 vs. 100 msec),
 - temperature (35–37°C vs. room temperature)



Clinical inference limitations of *in vitro* studies (1/2)

- When antibiotics are administered *in vivo*, there are many additional factors that can modulate drug effects on the heart :
 - Both erythromycin and clarithromycin both bind to plasma proteins in a concentration-dependent manner, and are ~ 50% bound at concentrations near their IC50 for HERG blockade].
 - Therefore, it would be expected to decrease the percentage of drug readily available for interaction with ion channels.
 - However, both drugs have also been reported to accumulate intracellularly in tissues at concentrations several fold higher than those in the plasma. This phenomena could « over compensate » for the decrease in unbound drug in the plasma produced by interaction with plasma proteins.



Clinical inference limitations of in vitro studies (2/2)

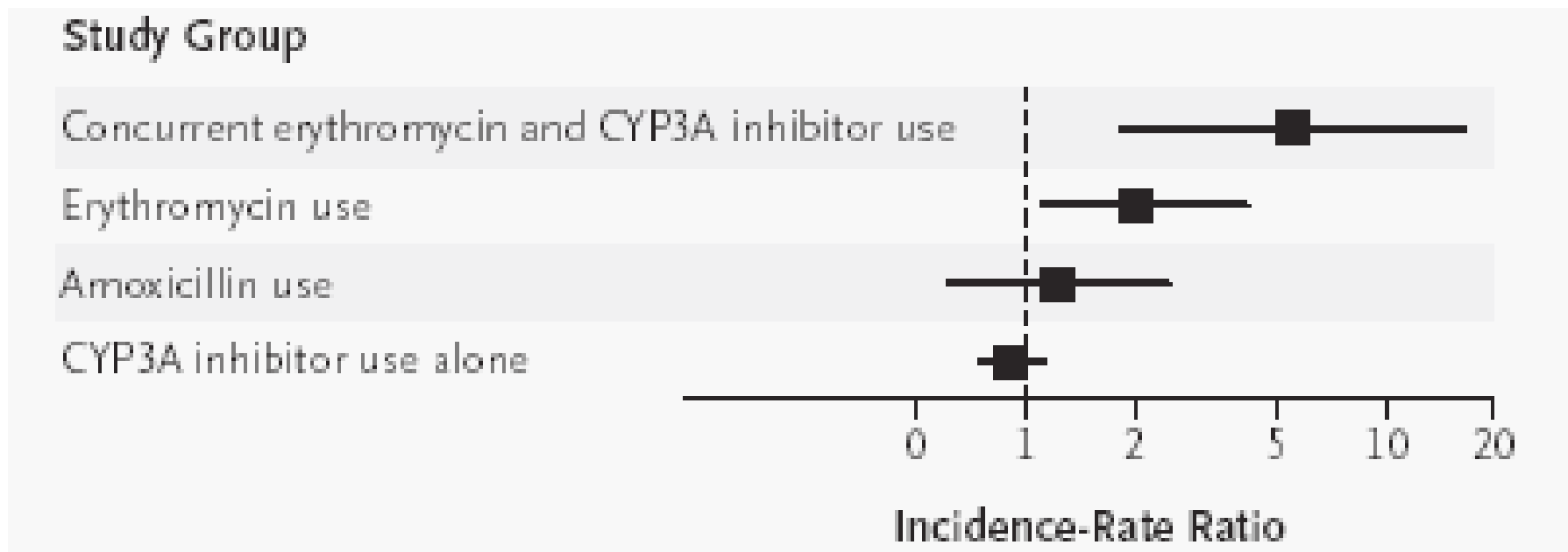
- Both antibiotics also undergo significant hepatic metabolism, and it remains unclear whether metabolites that can accumulate with repeated dosing also contribute to channel blockade, or alternatively are inactive as channel blockers.
- Other clinical abnormalities such as hypokalemia, hypomagnesemia, genetic polymorphisms of ion channel subunits, or other disease states may also contribute to drug-induced QT prolongation in the clinical setting.
- Therefore it is most prudent to conclude that the results of the current study indicate that both antibiotics have the potential for directly producing significant ion channel blockade at clinically relevant conditions.



Incidence-Rate Ratio for Sudden Death from Cardiac Causes, according to Antibiotic Use

Antibiotic Use	Person-Years <i>number</i>	Deaths	Incidence-Rate Ratio (95% CI)	
Current use of erythromycin	5,305	10	2.01 (1.08–3.75)	←
Current use of amoxicillin	6,846	8	1.18 (0.59–2.36)	←
Former use of erythromycin	111,779	100	0.89 (0.72–1.09)	←
None	1,126,013	1358	1.00	

The Incidence-Rate Ratio for Sudden Death from Cardiac Causes according to the Current Use of the Study Antibiotic Medications and CYP3A Inhibitors.





Official warnings reported in safety labels of marketed macrolides (CYP affinity)

- **group 1** includes erythromycin and troleandomycin, which bind strongly to and inhibit markedly the CYP3A4;
- **group 2** includes clarithromycin, roxithromycin, josamycin, miocamycin and midecamycin, which exhibit lower affinity for the CYP3A4 as compared with erythromycin, and form complexes to a lesser extent;
- **group 3** includes azithromycin, dirithromycin, spiramycin and rokitamycin, which have been shown to interfere poorly with the cytochrome P450 system.

Official warnings reported in safety labels of marketed macrolides

No. of atoms in the ring	Drug ^a	Official warnings		
		Gastrointestinal effect	Proarrhythmic effect (QT prolongation)	Inhibition of drug metabolism
14	Erythromycin	Yes	Yes	Yes (strong)
	Clarithromycin	Yes	Yes	Yes
	Roxithromycin	Yes	Yes	Yes
	Flurithromycin	Yes	Not mentioned	Yes
	Dirithromycin	Yes	Yes	Yes
15	Azithromycin	Yes	Yes	No ^b
16	Midecamycin	Yes	Not mentioned	Not mentioned
	Miocamycin	Yes	Not mentioned	Yes (high concentrations)
	Acetyl-spiramycin	Yes	Not mentioned	No
	Rokitamycin	Yes	Not mentioned	No (with theophylline)
	Josamycin	Yes	Not mentioned	Yes
	Telithromycin	Yes	Yes	Yes



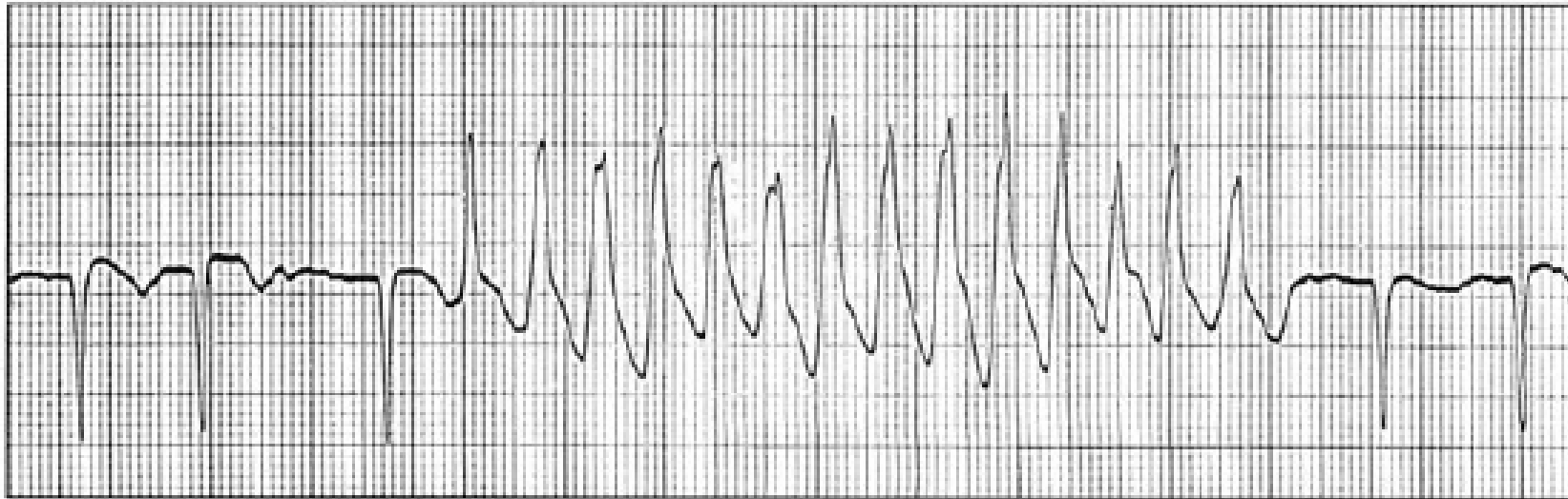
QT prolongation & TdP by Antimicrobial class

- Macrolides, azalides, ketolides
- **Fluoroquinolones**
- Azoles
- Miscellaneous
 - Cotrimoxazole
 - Pentamidine
 - Clindamycine

Fluoroquinolones & TdP : quelques repères

- **Sparfloxacin** : « noyées » dans les problèmes de photo-toxicité et de tendinopathies, 3 TdP rapportées dès la première année d'utilisation « franco-française » (environ 1 M de prescription)
- **Grépafloracin** : décision de retrait par la firme en raison de morts subites présumées rythmiques
- **Moxifloracin** : « saga » réglementaire » d'un produit depuis devenu la référence en matière de témoin positif dans les « études ECG intensives » de phase 1 (ICH E14), alors même que l'incidence des TdP reste faible
- **Levofloracin** : isomère lévogyre de l'ofloracin dont il concentre efficacité ... et effets cardio-toxiques

QT prolongé, TdP, ACFA, levofloxacin



Cardiac effect of Fluoroquinolones

Agent	Substituent at Position 5	QT Prolongation (ms)
Sparfloxacin	Methyl	14
Grepafloxacin	Amino	11
Moxifloxacin	Hydrogen	6
Levofloxacin	Hydrogen	5
Gemifloxacin	Hydrogen	3
Gatifloxacin	Hydrogen	3
Ciprofloxacin	Hydrogen	< 2

Quinolones : risk of cardiotoxicity per 10 million patients treated

Agent	Number of Cases
Moxifloxacin	4 (in 13 million)
Ciprofloxacin	8
Ofloxacin	18
Levofloxacin	18
Gatifloxacin	27 (8 in 3 million)
Gemifloxacin	Not yet used in United States; data unavailable
Sparfloxacin	> 100
Grepafloxacin	> 150

*Defined as torsades de pointes, ventricular tachycardia, or bradycardia.

MedWatch data from the FDA 1999 Pink Sheet adapted to May 2001.

Risk of TdP associated with Fluoroquinolones

Agent	FDA Cases in United States	Prescriptions in United States (millions)	Cases per 10 Million Prescriptions (95% CI)	P Value
Ciprofloxacin	2	66	0.3 (0.0 - 1.1)	
Ofloxacin	2	9.5	2.1 (0.3 - 7.6)	
Levofloxacin	13	24	5.4 (2.9 - 9.3)	< .001*
Gatifloxacin	8	3	27 (12 - 53)	< .001†



Moxifloxacin : tolérance cardiaque – données extraites du dernier PSUR –

(au 30-05-2004 : plus de 30 millions de patients traités par voie orale)

- cas rapportés d'allongement de QT = 41

- cas rapportés de TdP =12
 - pour tous les cas, évolution favorable de l'épisode
 - 10F/2M
 - facteurs de risque associés chez tous les patients



Risk factors present in all previously published cases of fluoroquinolone-induced Torsades de Pointes (N = 8 patients)

<i>Drug</i>	<i>Patient risk factors</i>	<i>Concomitant drugs</i>
Gatifloxacin ⁷	Female, aged 79 years, bradycardia, hypomagnesemia	Sotalol
Gatifloxacin ⁸	Female, aged 81 years, heart failure, renal dysfunction*	Amiodarone
	Female, bradycardia (AV block)	Amitriptyline
	Aged 74 years, heart failure, renal dysfunction*	—
Levofloxacin ²⁴	Renal dysfunction,* pretreatment QTc interval prolongation (454 ms)	Amiodarone, imipramine
Levofloxacin ²⁵	Female, aged 88 years	Procainamide
Levofloxacin ²⁶	—	Amiodarone
	NR	NR

AV, Atrioventricular; *Gatifloxacin dose not appropriately adjusted for renal dysfunction.



from Amankwa K et al. – Clin Pharmacol Ther 2004;75:242-7

CPMP Safety Working Party (SWP)

Chairperson: Prof B. Silva Lima

SWP Report On The Cardiotoxicity Of Fluoroquinolones

(CO-ORDINATORS: DR. KLAUS OLEJNICZAK / DR. BERND ZÜNKLER)

- Fluoroquinolones with the potential of inducing TdP cardiac arrhythmia :

Clinafloxacin
Gatifloxacin
Gemifloxacin

Grapafloxacin
Moxifloxacin
Sparfloxacin

- Fluoroquinolones without the potential of inducing TdP cardiac arrhythmia :

Alatrovafloxacin
Ciproxacin
Levofloxacin

Ofloxacin
Trovafloxacin

- Pertinent information lacking :

Pefloxacin
Rufloxacin

Enoxacin
Fleroxacin
Lomefloxacin



QT prolongation & TdP by Antimicrobial class

- Macrolides, azalides, ketolides
- Fluoroquinolones
- **Azoles**
- Miscellaneous
 - Cotrimoxazole
 - Pentamidine
 - Clindamycine

Azoles & QTprolongation/TdP

- Effet modeste « per se »
- Puissants inhibiteurs
 - CYP3A4
 - Keto = Itraco > Vorico > Fluco
 - CYP2C9
 - CYP2C19
- Allongement considérable QT et TdP principalement en association avec d'autres molécules « potentes » (terfenadine, cisapride)

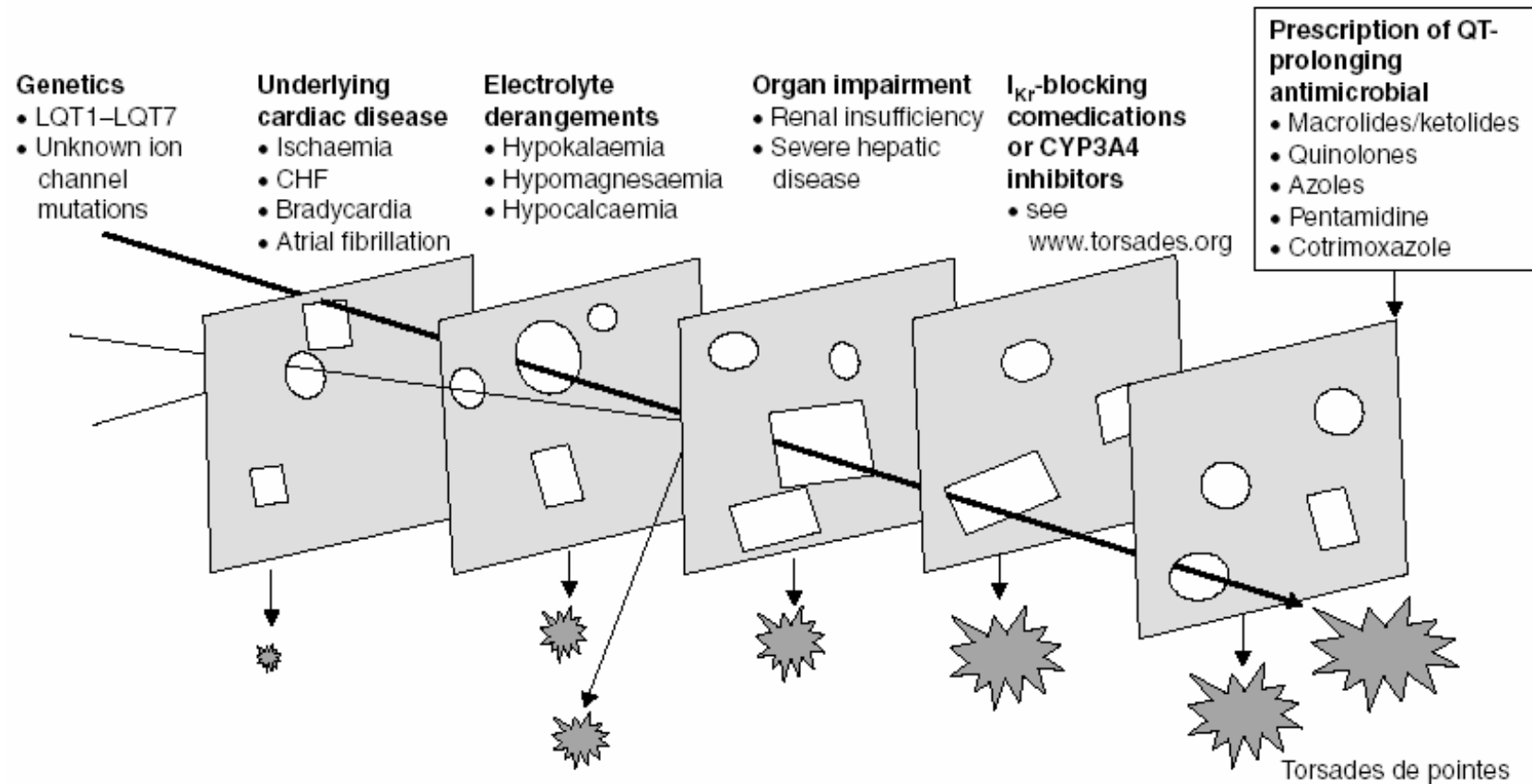


QT prolongation & TdP by Antimicrobial class

- Macrolides, azalides, ketolides
- Fluoroquinolones
- Azoles
- **Miscellaneous**
 - Cotrimoxazole : no evidence
 - Pentamidine : 13 TdP
 - Clindamycine : 1 TdP

Conclusion (1/2)

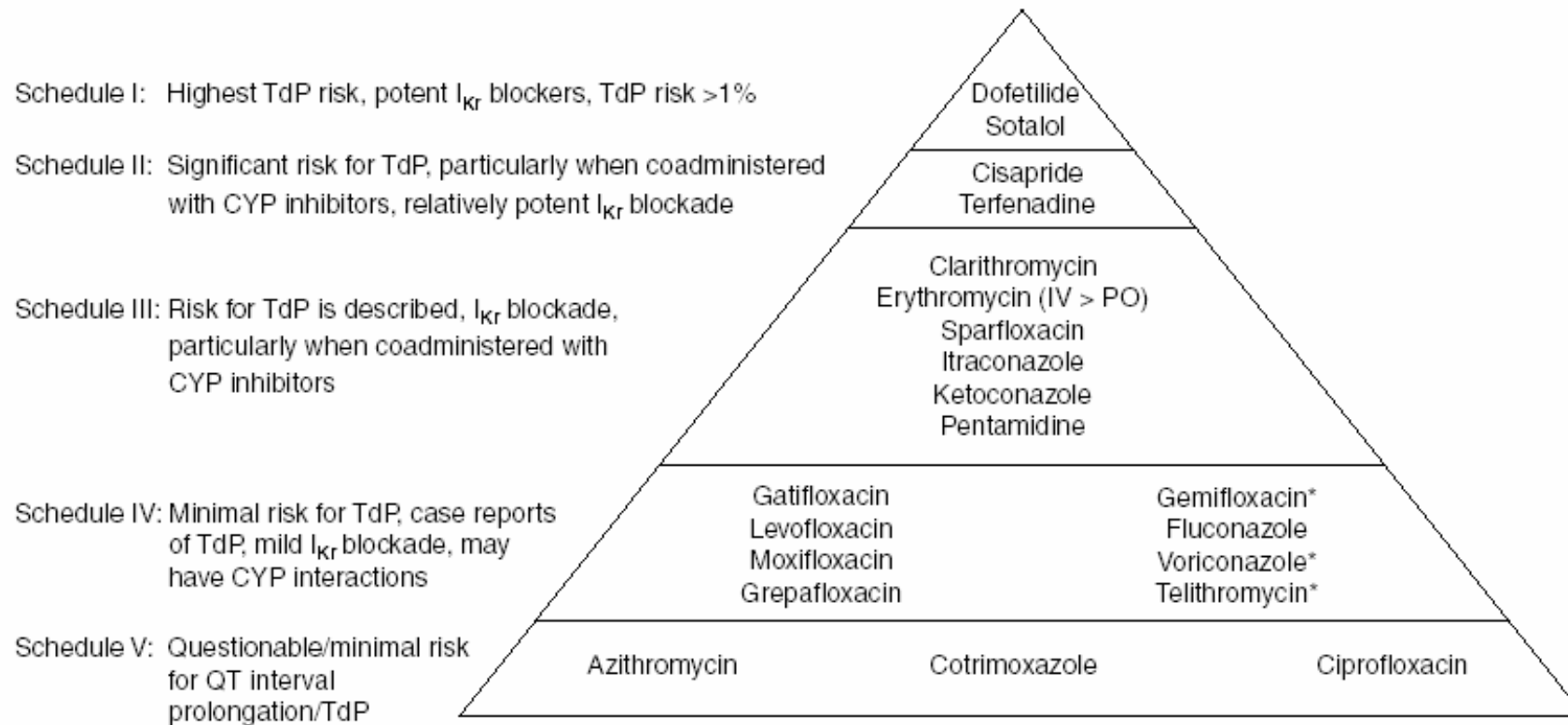
Multiple risk model for antimicrobial-associated torsades de pointes.



CHF = congestive heart failure; **CYP** = cytochrome P450; **IKr** = rapid component of the delayed rectifier potassium current; **LQT1–LQT7** = long QT genotypes.

Conclusion (2/2)

Torsades de pointes (TdP) : risk stratification for antimicrobial agents



CYP = cytochrome P450; **IKr** = rapid component of the delayed rectifier potassium current