

# **The Critical Path & Cardiac Safety 2009**

## **International View**

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Cardiac safety is currently and will in the foreseeable future be addressed the same way in EU as in US

This presentation will therefore share some personal thoughts on drug development and CV safety

## Critical Path -

to identify gaps in or knowledge that need to be addressed if we are to develop safe drugs more effectively

- Reduce drug development time/cost/expenditure
  - ✓ clinical outcome is the most costly endpoint
- Promote well-informed project prioritization in early stage based on surrogate endpoints
  - ✓ to avoid having to use clinical outcomes data as the only basis for decisions
- We may have to accept making decisions at an ‘exploratory’ confidence level
- Places emphasis on the need for an increased R&D productivity measured as delivery of more ‘high-quality’ candidate drugs

# Let's agree on what constitutes a failure!!

- Withdrawals of marketed drugs, e.g. mibefradil after 1 years because of underestimation of clinical significance of DDIs
- Non-approvals based on difference in risk-benefit assessment between regulators and sponsor, e.g. ximelagatran and muraglitazar
- Unexpected adverse clinical outcome in confirmatory trials, e.g. torsetrapib

**These are all failures not because we necessarily did something wrong but because we failed to do something better**

# Muraglitazar, cont.

**Table 4. Event Rates and Relative Risks**

	No. (%)		Relative Risk (95% CI)	P Value
	Muraglitazar (n = 2374)	Control (n = 1351)		
<b>Composite End Points</b>				
All-cause mortality plus nonfatal MI or stroke	35 (1.47)	9 (0.67)	2.23 (1.07-4.66)	.03
All-cause mortality plus nonfatal MI, stroke, CHF, or TIA	50 (2.11)	11 (0.81)	2.62 (1.36-5.05)	.004
Cardiovascular death plus nonfatal MI or stroke	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death plus nonfatal MI, stroke, CHF, or TIA	42 (1.77)	9 (0.67)	2.82 (1.30-5.53)	.007
All-cause mortality or nonfatal MI	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death or nonfatal MI	19 (0.80)	5 (0.37)	2.17 (0.81-5.83)	.12
<b>Individual End Points</b>				
All-cause mortality	15 (0.67)	3 (0.22)	3.05 (0.89-10.5)	.08
Cardiovascular death	8 (0.34)	1 (0.07)	4.57 (0.57-36.5)	.15
Fatal or nonfatal MI	15 (0.63)	4 (0.30)	2.14 (0.71-6.46)	.18
Fatal or nonfatal stroke	9 (0.38)	2 (0.15)	2.57 (0.55-11.9)	.23
Fatal or nonfatal TIA	5 (0.21)	1 (0.07)	2.85 (0.33-24.4)	.34
Adjudicated CHF	13 (0.55)	1 (0.07)	7.43 (0.97-56.8)	.053
Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.				

Nissen, Lancet 2005; 294: (doi:10.1001/jama.294.20.joc50147)

# Case example 1 –

combining non-clinical and clinical data can accurately predict cardiac risk on a population level

## QT prolongation and proarrhythmic risk

### We are here:

NC data has some value

Early clinical data has some value

TQT study regarded as definitive evidence

### We would like to be here:

Non-clinical data have large value

Early clinical data regarded as confirmatory

**Step 1:** Stop blaming the regulators;

**Step 2:** Stop blaming the biomarker – find and validate a better one!

**Step 3:** Design assays/studies and collect data that are convincing  
and address existing concerns (which are known)

# **QT prolongation and proarrhythmic risk**

## **Concerns (non-exclusive list)**

### **1. NC data has not sufficiently high -predictive value:**

- a. Improve precision in safety pharmacology studies

### **2. Early clinical data has not sufficiently high -predictive value:**

- a. Test different PK/PD models on TQT data to learn more about strengths and weaknesses of models and how the result relate to traditional E14 endpoints
- b. Learn how to apply these models on pooled early clinical data;
- c. Validate vs. TQT results
- d. Explore the richness of ECG data (80 000 beats vs. 72)

### **3. Demonstration of assay sensitivity in early clinical studies**

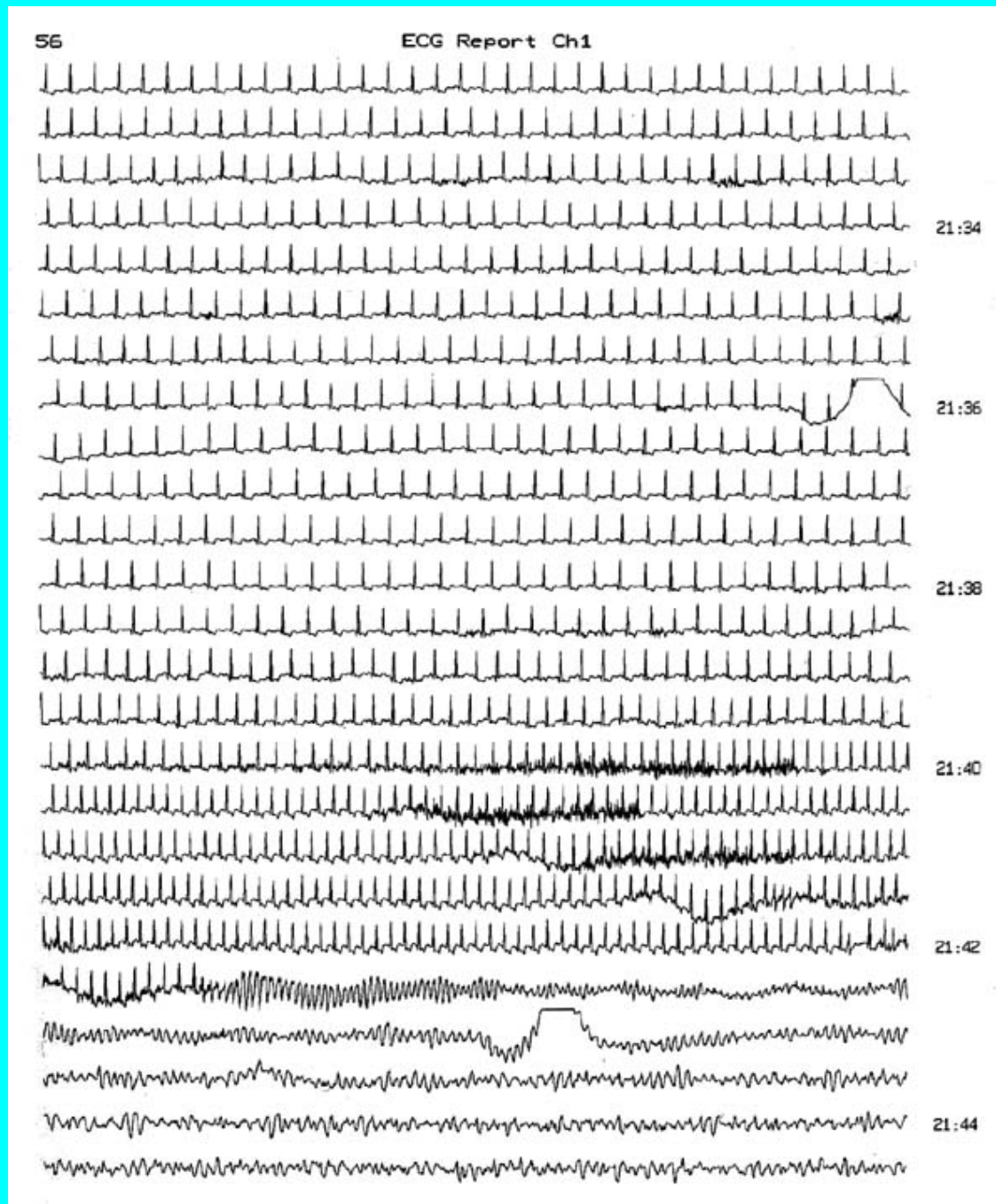
- a. Explore non-pharmacological ways to establish assays sensitivity

# **QT prolongation and proarrhythmic risk**

- 1. Work with regulators with an interest to collaborate**
  
- 2. This is largely a data driven environment**
  - a. It is up to industry to collect convincing data



This Sudden death  
was not caused by  
drug induced QT↑ !!



# Case example 2 –

combining non-clinical and clinical data can accurately predict cardiac risk on a population level

## Increased blood pressure and increased CV risk

### We are here:

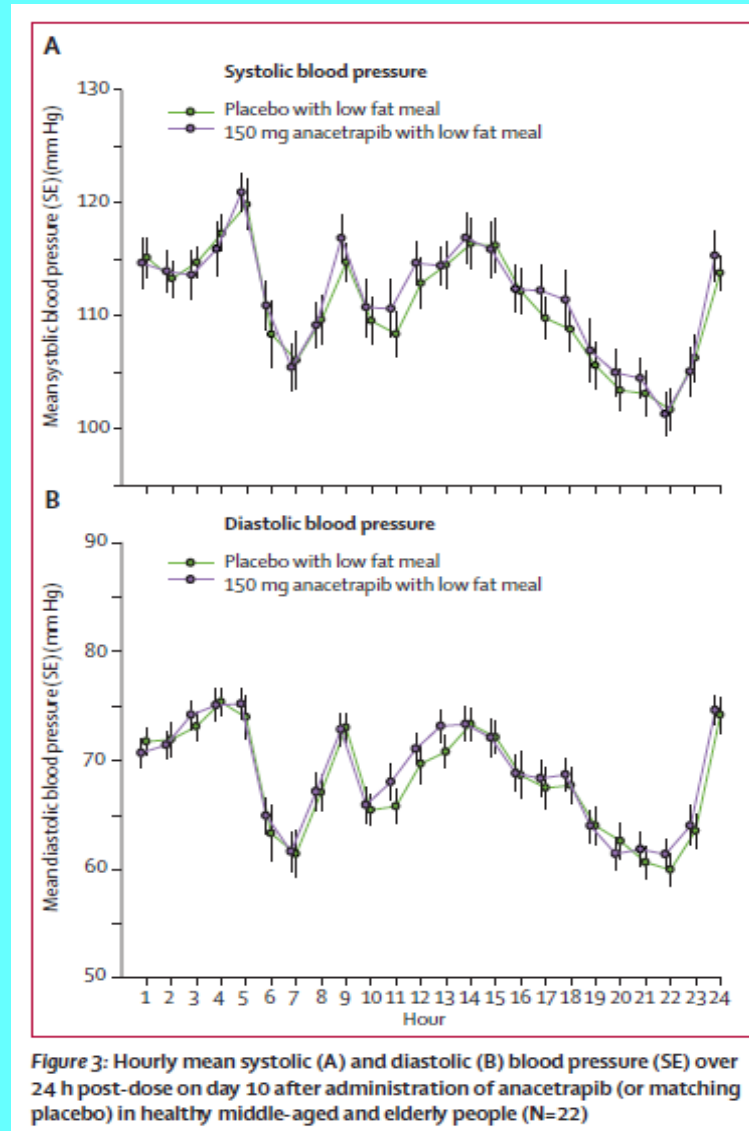
- Broad agreement that an increase in BP, if not transient, is associated with a population-based increased CV safety risk
- No reason to believe that a BP $\uparrow\uparrow$  (in most cases) is of benefit in terms of CV safety

# ↑ Blood pressure and ↑ CV risk

Let's utilize  
the richness  
of the data:

Ambulatory BP monitoring  
in HVs can be incorporated  
in early clinical trials

From:  
Krishna, Lancet 2007; 370: 1907-14



# When things are getting more complicated....

## Cardiomyocyte toxicity and cardiac troponins

### The value of cTn is clearly demonstrated

- for diagnosis and handling of patients with AMI/ACS
- to show drug effects in certain settings, e.g. protective effect of dexrazoxane in children Tx with doxorubicin
- Emerging new, highly-sensitive assays for cTn may seem to make this biomarker even more ideal for monitoring of cardiomyocyte toxicity in drug development

# Cardiomyocyte toxicity and cardiac troponins

## Clinical issues that need to be addressed (non-exclusive):

- Predictive values outside ACS area needs to be better characterized
- Specificity of cTn outside ACS area, e.g. non-cardiac sources for cTn elevation, e.g. renal failure, other cardiac diseases/procedures, trauma, inflammatory conditions;
- Several available assays for cTn isoform I with differences in reference values and sensitivity
- The variability of highly sensitive cTn in both HVs and in patients is unexplored and not well characterized.
- Ethically challenging to take a drug with a cTn ‘signal’ into FIM trials

# What do I see in my crystal ball?

- Integration of several NC disciplines (pharmacology, toxicology, safety pharmacology) for the assessment of CV risk
- A substantially expanded role for safety pharmacology
- Broader application of select biomarkers for CV risk in exploratory clinical development