Cardiac Safety Workshop
Key Issues and Best Practice for Thorough QT Studies and Intensive Phase I QT Studies

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CoreLab PARTNERS
RICHMOND Pharmacology

St George's University of London

Introduction

- We asked you to provide us feedback so we could focus our workshop around your interests
- We have structured these under three main headings:
  - The current regulatory framework (rules)
  - The current state of the art (how)
  - The contemporary and future anticipated developments (future)
- We will give short presentations under each main heading, allowing for discussion under each point
- We have 90 minutes

Rules

Be aware of the current cardiac safety **regulatory** framework **3x**

Understand the key ICH-E14 requirements for cardiac safety assessments **3x**

Appreciate the "**regulatory** awareness threshold" for drug-induced QT prolongation **1x**

Be aware of recent **regulatory** expectations for additional ECG parameters during the QT study **2x**

How

Have a basic understanding of the **development process** and **design** of the TQT study **3x**

Other QTc formula than Bazett's or Frederica's... Necessity of **positive controls** **[**Alternatives to standard TQT**]**

Model and simulations. **Concentration-QT analyses**

highly-automated QT measurement techniques versus semi-automated

Regulatory requirements for the TQT **studies in patients studies** which can not be blinded for ethical reasons

Future

How to identify **drugs that might have a potential for QT prolongation**, respectively, how to successfully argue that **checking** this potential safety problem **is not necessary**.

Recognise the benefits and limitations of ECG assessments in **other, none-TQT, Intensive ECG/QT studies** **2x**

how high quality data produced during **early phase of development** might be used to discharge the risks, and/or to be used for setting up better TQT trials. View on the use of the **positive control**

relevance of increase of **secondary endpoints** (eg. HR) for regulatory bodies

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Background

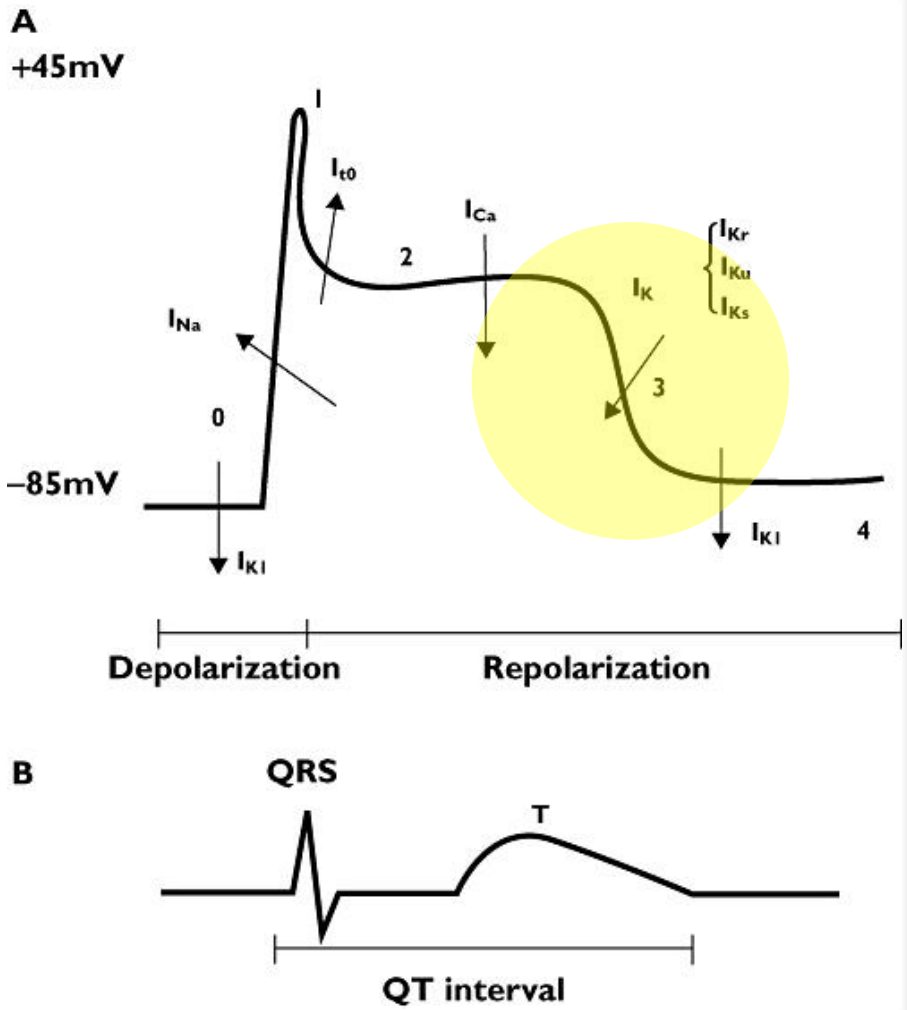
- Between 1991 and 2003, six drugs including terfenadine were withdrawn from the market because of an increased risk of Torsades de Pointes (TdP)
- Regulatory efforts started in 1997 with CPMP document “points to consider” and in 2005 culminated in the **ICH E14** guideline
- Since two **Q&A documents** were issued: **2008** and **2012**
- A pre-clinical guideline **ICH S7B** was adopted in 2005

Key Principles

- Thorough QT (TQT) studies are confirmatory biomarker studies that have one single aim:
- TQT studies aim at identifying those medicines that have no involvement in myocardial repolarization.
- Only such medicines identified having no involvement in myocardial repolarization can safely be considered as having no danger of drug induced arrhythmias such as TdP.
- TQT studies cannot quantify risk.

Cardiac cell action potential (aP)

- Most drug induced QT prolongations are related to a blockade of the rapid component of the delayed rectifier potassium channel (I_{kr}) which is encoded by the human ether a go-go related gene (*hERG*)



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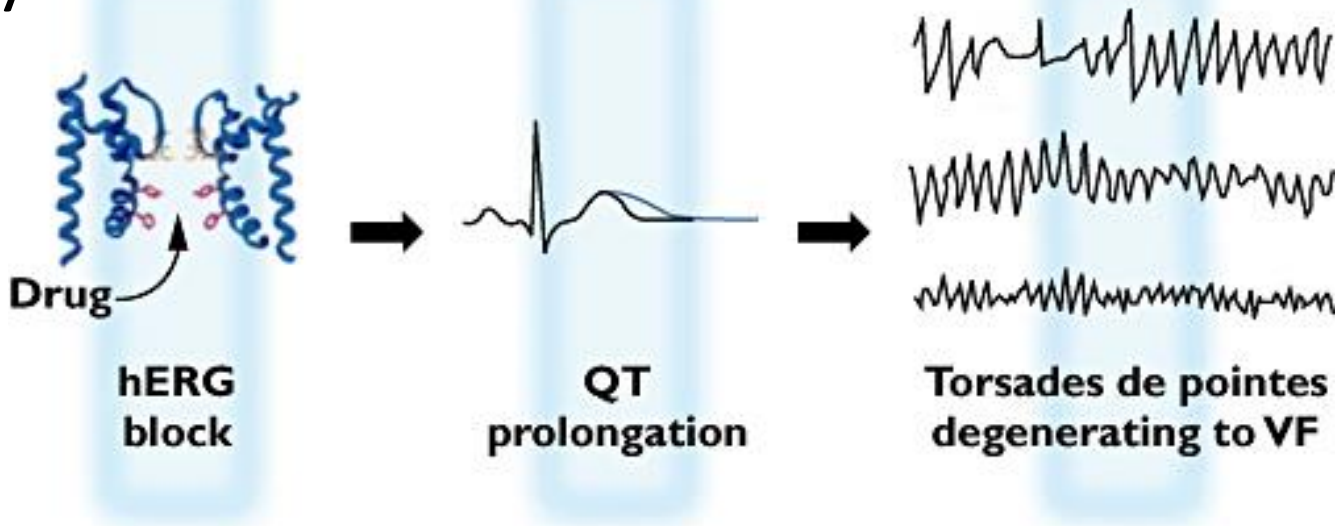
Use of QT as a Biomarker

- Ikr blockade will change the action potential,
- This leads to a prolongation of the QT interval in the ECG
- This ***may*** lead to TdP which in turn (some drugs associated with QT_c prolongation are devoid of torsado-genic effects) which ***can*** deteriorate to lethal arrhythmias such as VT



From:
Br J Clin Pharmacol. 2010 July; 70(1): 16–23.
doi: 10.1111/j.1365-2125.2010.03660.x

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ICH S7B

- Objective: non-clinical testing strategy for assessing the potential of a drug to delay ventricular repolarization
- Integrated risk assessment including:
  - In vitro IKr assay (hERG)
  - repolarisation assay Purkinje fibre
  - In vivo QT assay
- hERG safety margin 45 predicts the absence of a QT effect with a sensitivity of 64% and specificity of 88% (Gintant 2011).

ICH E14 Interpretation

- *"A negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms.*
- *This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5msec, which is the threshold level of regulatory concern"*
- Phase III:
  - If TQT negative = routine monitoring
  - If TQT positive = additional ECG assessments

Phase III ECG monitoring

- *Monitoring needed?*

TQT Result	Likely or possible exposure of patients to similar concentrations	Un-likely exposure of patients to similar concentrations	Exposure in a limited well defined sub-population of patients only
TD = negative ST = 10-20ms prolongation	[YES]	NO	YES (for the subset)
TD > 20ms prolongation	YES	YES	N/A (NB: Risk mitigation)

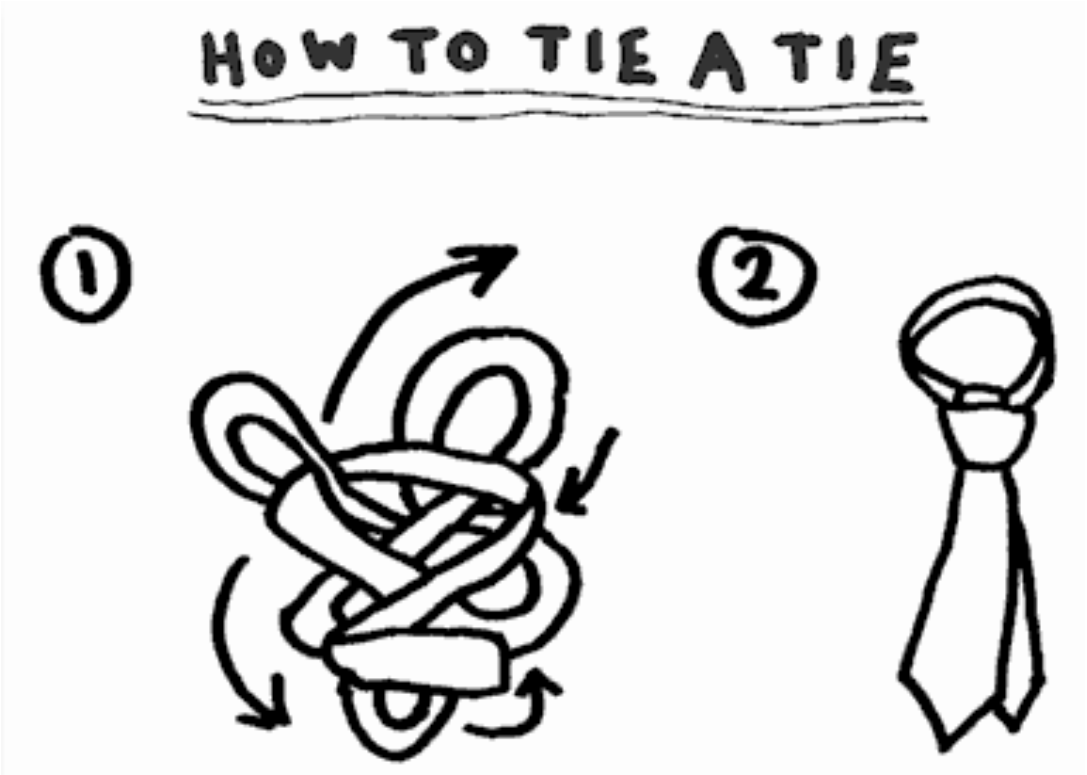
- *Local monitoring*
- *Intensive monitoring*

FDA received **post-marketing reports** of QT interval prolongation ***and*** Torsade de Pointes associated with Celexa (citalopram)

Citalopram		**Escitalopram**	
Dose ***New (restricted) maximum daily dose.**	**Change in QTc (90% CI) [ms]**	**Dose**	**Change in QTc (90% CI) [ms]**
20 mg	8.5 (6.2, **10.8**)	10 mg	4.5 (2.5, 6.4)
40 mg*	12.6 (**10.9**, **14.3**)	**20 mg***	6.6 (5.3, 7.9)
60 mg	18.5 (**16.0**, **21.0**)	30 mg	10.7 (8.7, **12.7**)
Moxifloxacin 400 mg	13.4 (**10.9**, **15.9**)	Moxifloxacin 400 mg	9.0 (7.3, **10.8**)

Recognition that although citalopram use should be avoided, if possible, in patients with certain conditions because of the risk of QT prolongation, ECG monitoring and/or electrolyte monitoring should be performed if citalopram must be used in such patients.
Patients with congenital long QT syndrome are at particular risk of Torsade de Pointes, ventricular tachycardia, and sudden death when given drugs that prolong the QT interval. Nevertheless, the labeling recommendation for patients with congenital long QT syndrome has been changed from "contraindicated" to "not recommended," because it is recognized that there may be some patients with this condition who could benefit from a low dose of citalopram and who lack viable alternatives.
The maximum recommended dose of citalopram is 20 mg per day for patients older than 60 years of age.
Citalopram should be discontinued in patients who are found to have persistent QTc measurements greater than 500 ms.

Source: FDA.gov; with thanks to B Tyl



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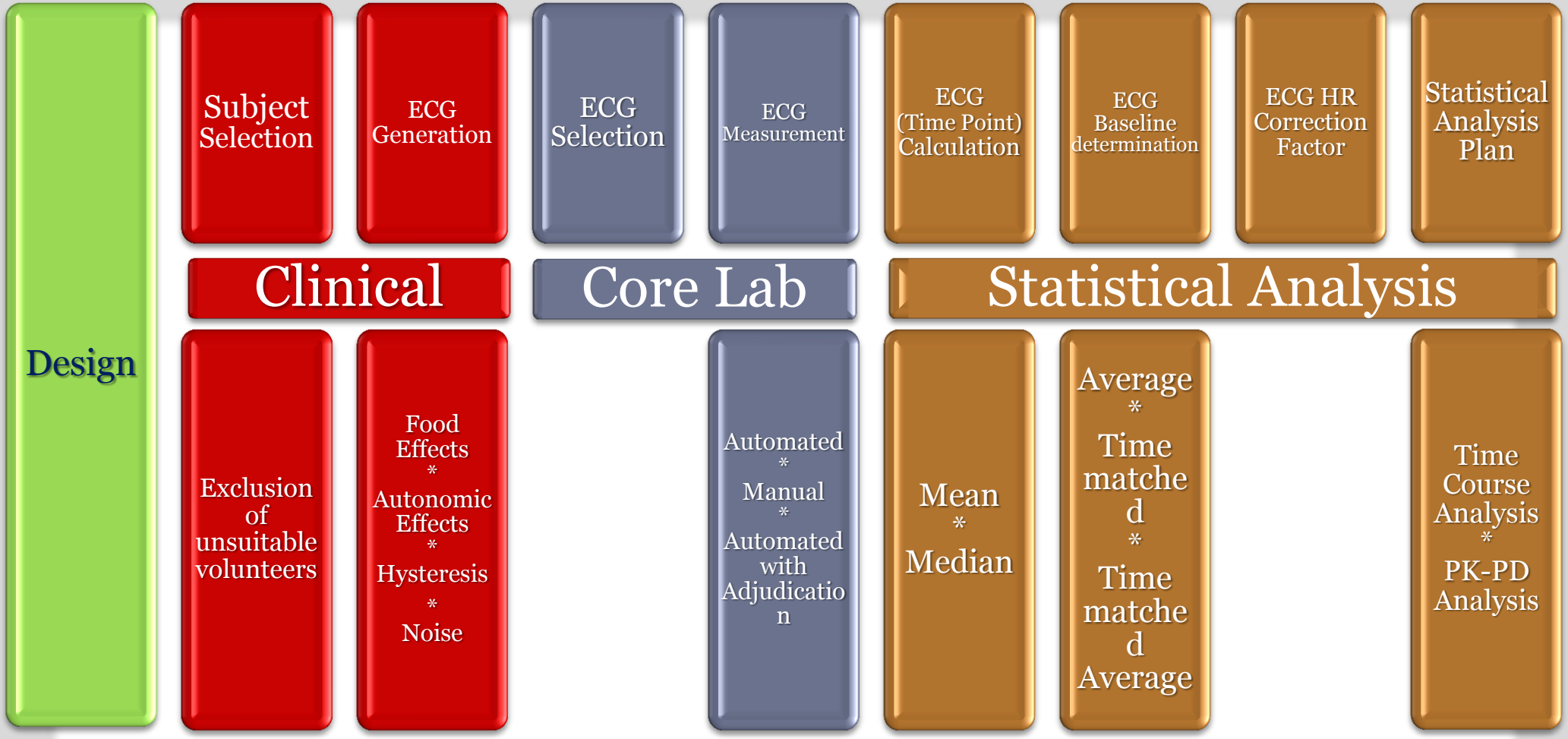
Running a TQT Study - Points to Consider



Regulatory Acceptance

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Typical Study Design

Design

- Typically 4 treatment arms
  1. Placebo
  2. Positive control (400mg moxifloxacin)
  3. Therapeutic Dose
  4. Supra-Therapeutic Dose

Study Design

Typically:

	Single use	Chronic use
Short t1/2	4-way cross-over	*Consider: metabolites*
Long t1/2	*Consider: practical aspects*	4 group parallel design*

*Consider nested cross-over design

Challenges

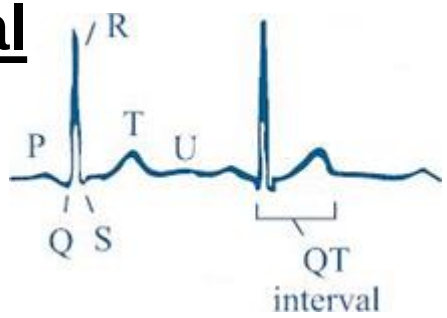
Design

- Failure to show assay sensitivity
- Exposure (dose) to low to cover patient use
- …

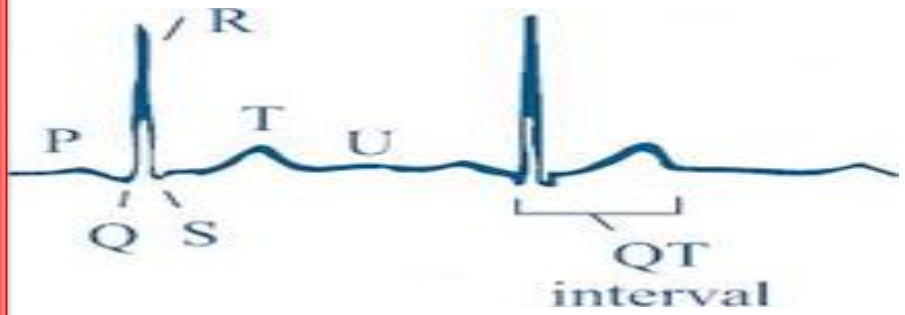
QT-RR Hysteresis

CLINICAL TASKS

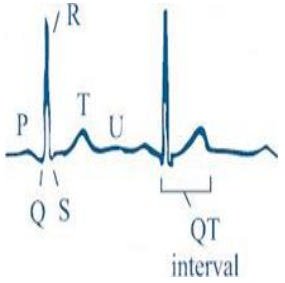
Normal

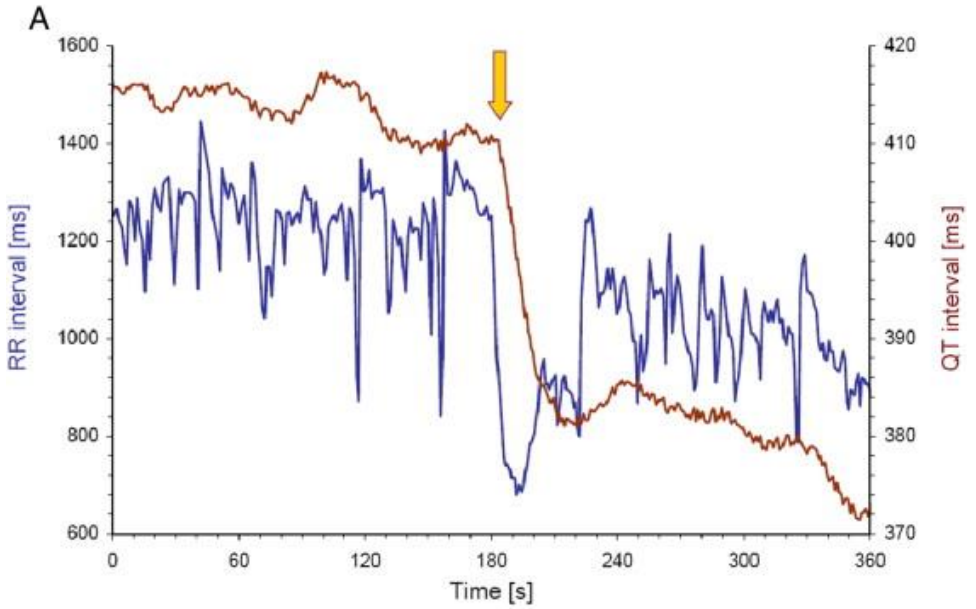


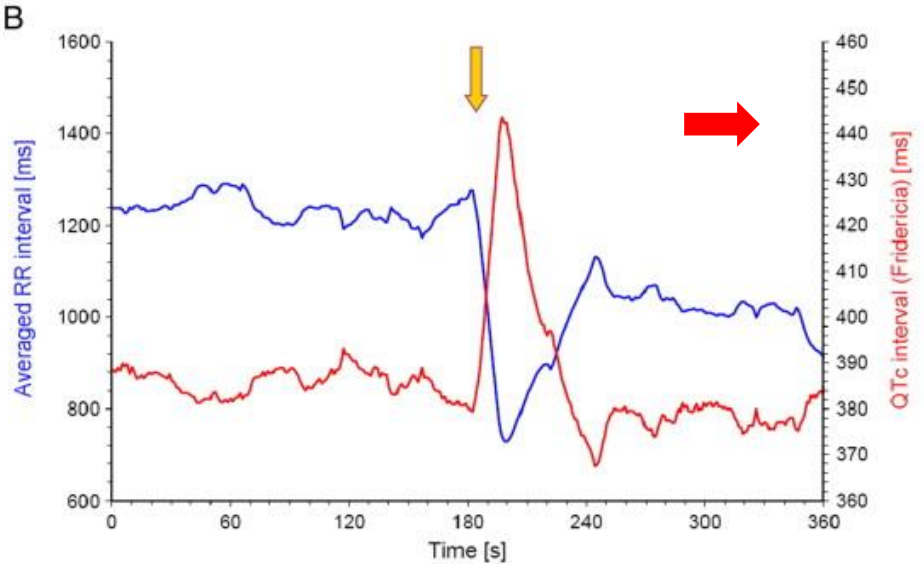
Slow



Fast







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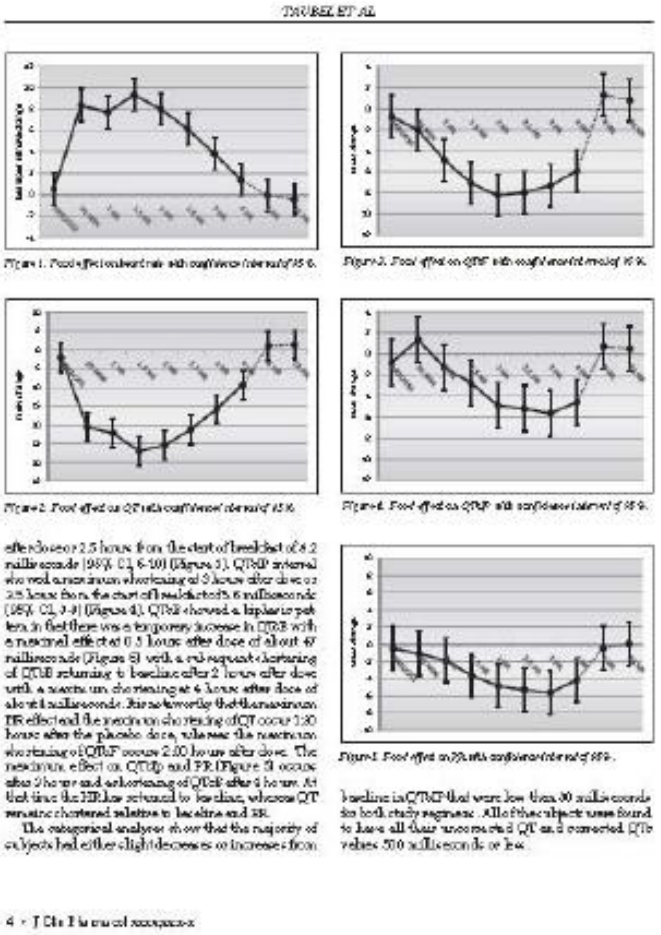
Meals shorten QTcF by 8-10 msec

CLINICAL TASKS



1. Increase in heart rate
2. Shortening of the QTc interval
3. Similar result QTcF/QTcI
4. We speculated that the effect may be caused by a release of c-peptide, more likely than autonomic.

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Sleep prolongs QTcF by ~20 msec

CLINICAL TASKS

- The difference in Q-T interval between awake and sleep states was 19 +/- 7 ms when calculated at a heart rate of 60 beats/min.

From:
Prolongation of the Q-T interval in man during sleep.
Browne KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP.
Am J Cardiol. 1983 Jul;52(1):55-9.

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False Signals of QTc Change

- The measurements are technically correct
- But they measure something other than a drug effect.

CLINICAL TASKS

Practical Considerations

- Subject selection
- Clinical conduct:
  - Avoid heart rate changes
  - Avoid autonomic effects
  - Avoid sleep
  - Control food effects
- Technical
  - Lead changes
  - Electrical interference
  - WiFi transmission errors (Mortara)

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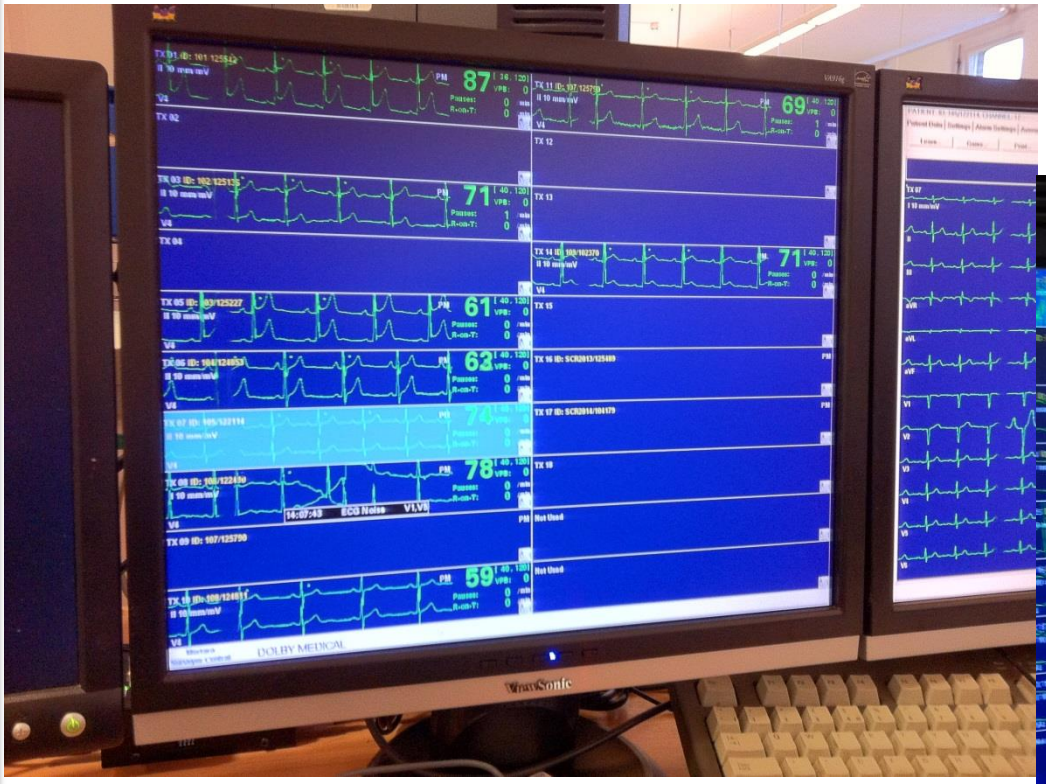
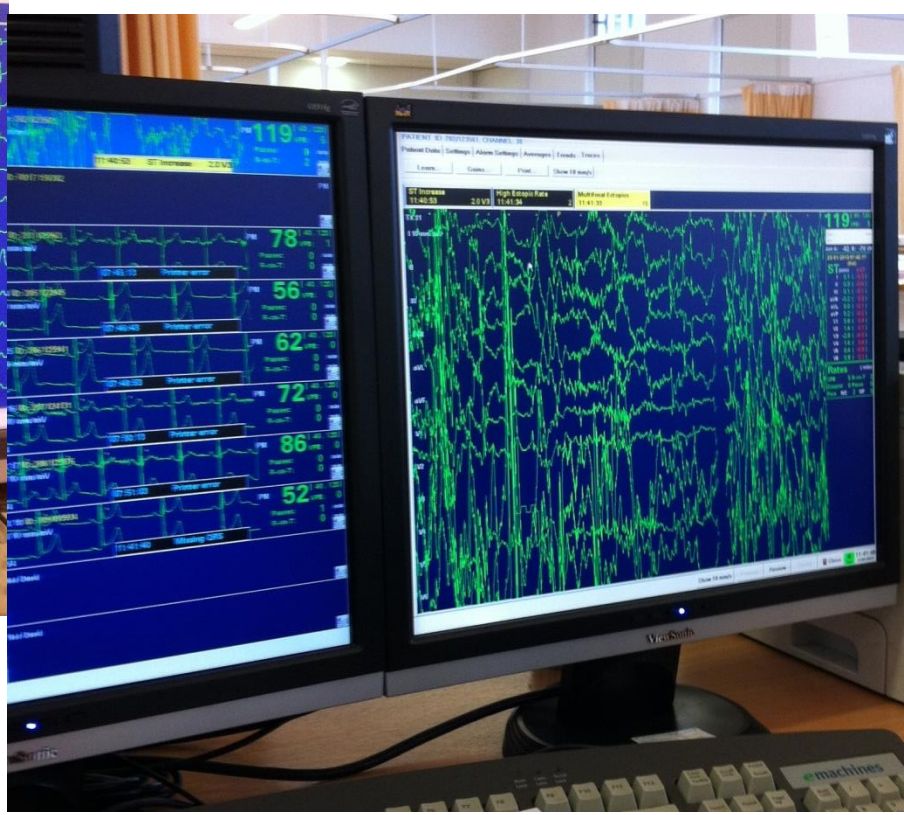
12L-Holter or Bedside ECG



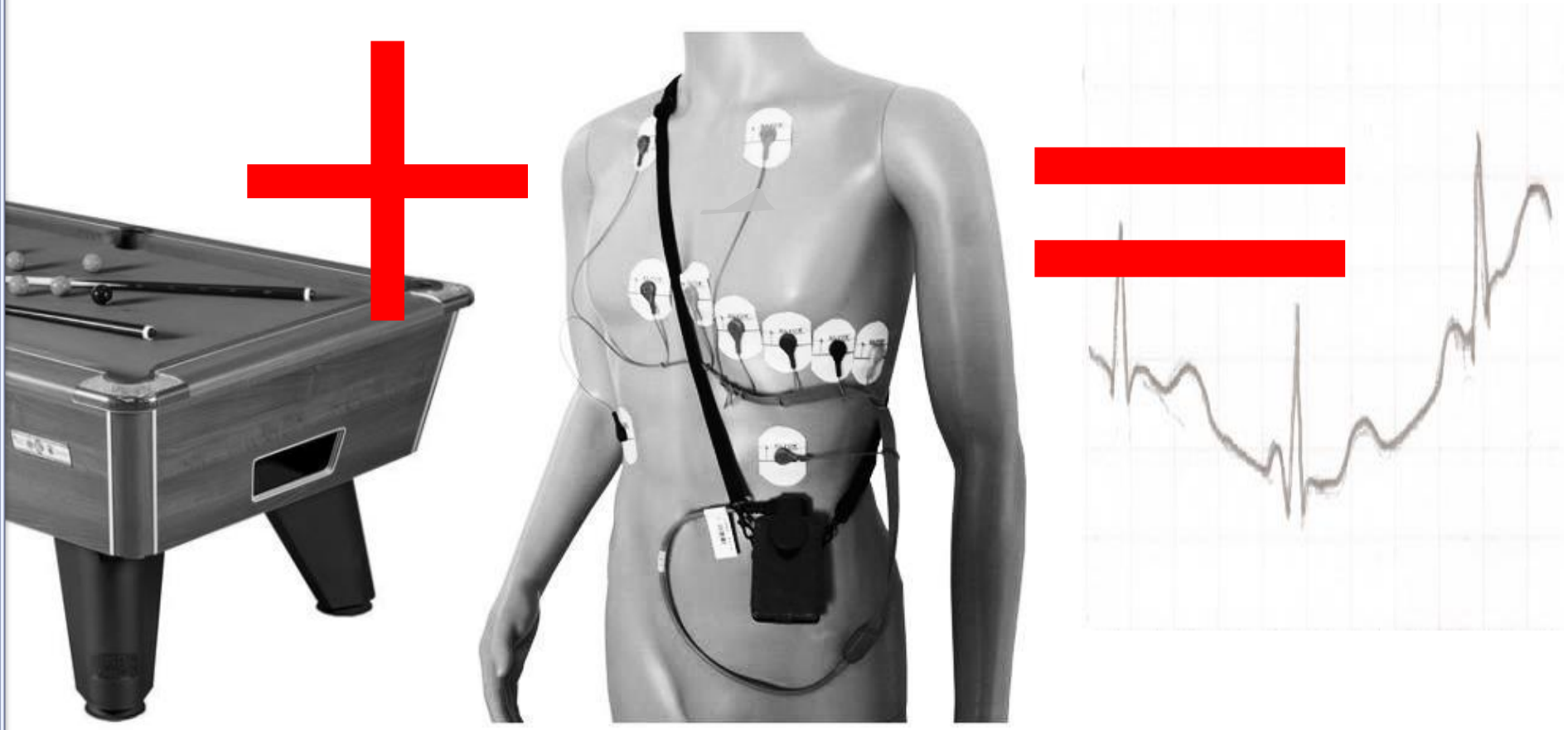


- Continuous and versatile
- Simple ?

12L-Holter or Bedside ECG

- Challenges:
  - QTc analysis depends on concentration data!
    - Extra ECG data may not correlate to PK data
  - Missing data
    - Batteries, lost data cards, transmission (WiFi) losses
  - Poor data
    - Artefacts
    - Volunteers changing leads
  - Events are difficult to correlate to events affecting QTc
    - It is usually unknown what a patient did at the time of a signal

Bad ECG Formula



Data Variability + Random Error

What you want

What you get

Compensatory increase in sample size

Will cost You $$$,$$$

"Don't worry we will fix it"

Or: Soil your washing …

… so you need more of my washing powder …

- **: Expensive**
- **: Real QTc changes that are not drug related cannot be removed that way.**

Automated Assessments

- Sections 2.5.1 and 2.5.2 of the ICH E14 Guideline are rather discouraging about methodology outside conventional carts and human-determined measurements.
- Since ICH E14 was issued, 12-lead continuous recording devices have largely supplanted cart recorders in thorough QT studies without a formal validation process because of their performance in the context of a positive control.

Other ECG Parameters

- Because changes in morphology can affect interval measurement, fully manual or manual adjudication (as defined in Question 4A) techniques should be performed if treatment-emergent changes in morphology are observed. If, on the other hand, no morphology changes are observed, this would support the use of automated methodologies, provided they have been validated.
- **QT Interval measurement**
- **T wave morphology assessment**

ICH E14 Assessments

- The techniques currently in use for the measurement of ECG intervals can be classified into three broad categories:
  - fully manual
  - fully automated
  - manual adjudication (manual over-read, computer-assisted, semi-automated)

ECG LABORATORY TASKS

Automated Assessments

- Dynamic Beat to beat (icardiac/Fossa)
- 12L Holter with subsequent extraction
- etc …

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STATISTICAL ANALYSIS

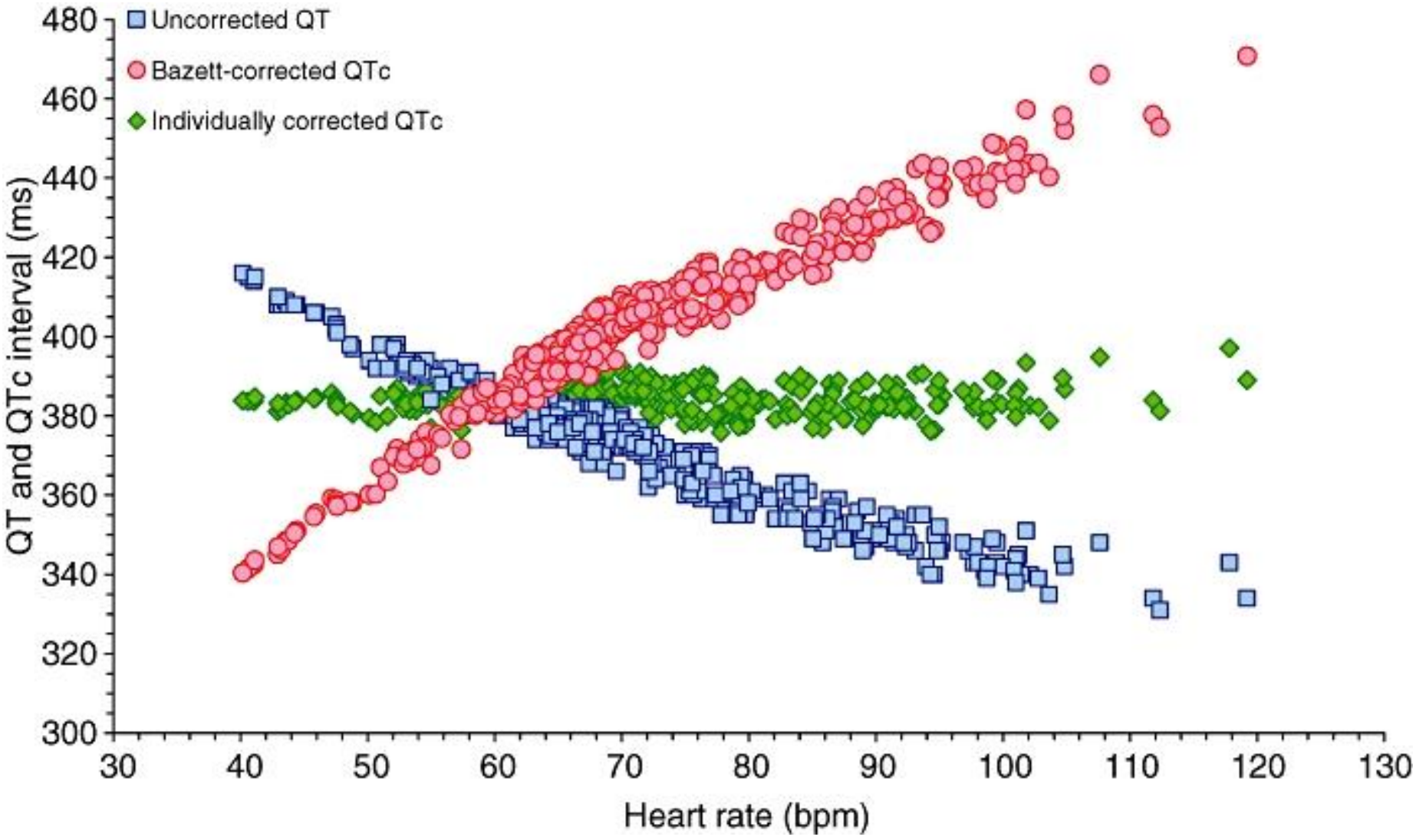
Analysis

$$\Delta QTc_{drug}(t) = QTc_{drug}(t) - QTc_{drug}(\text{baseline})$$

$$\Delta QTc_{placebo}(t) = QTc_{placebo}(t) - QTc_{placebo}(\text{baseline})$$

$$\Delta\Delta QTc(t) = \Delta QTc_{drug}(t) - \Delta QTc_{placebo}(t),$$

Heart Rate Corrections



From:
Malik M.: Facts, fancies and follies of drug-induced QT/QTc interval shortening
Br J Pharmacol. 2010 January; 159(1): 70–76.
doi: 10.1111/j.1476-5381.2009.00554.x

STATISTICAL ANALYSIS

Heart Rate Corrections

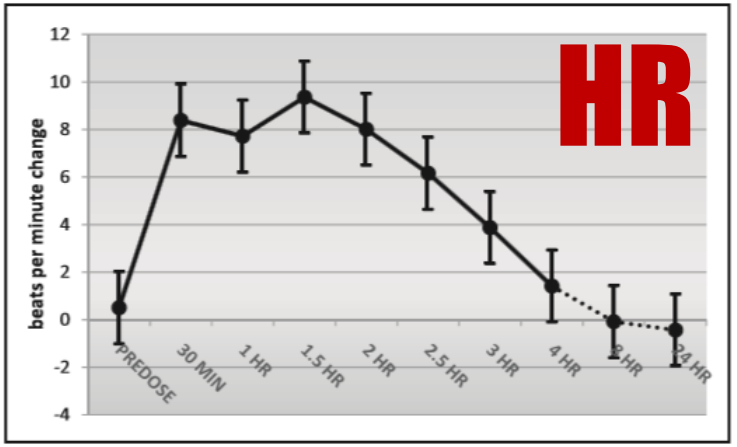


Figure 1. Food effect on heart rate with confidence interval of 95%.

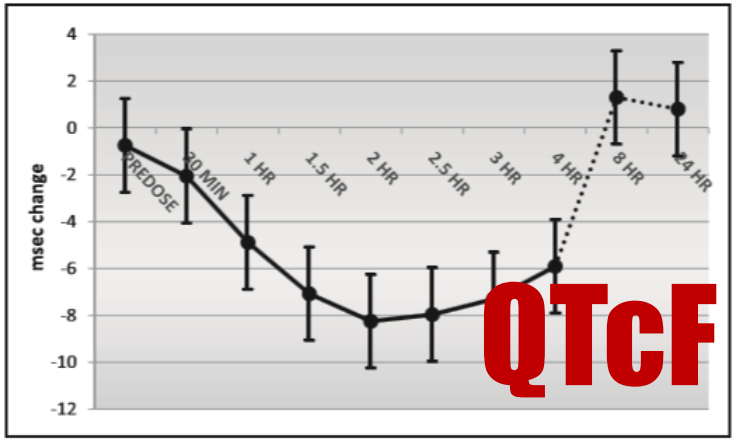


Figure 3. Food effect on QTcF with confidence interval of 95%.

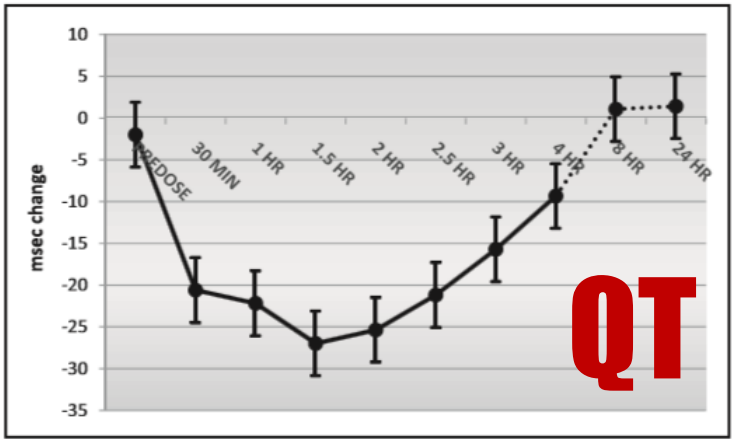


Figure 2. Food effect on QT with confidence interval of 95%.

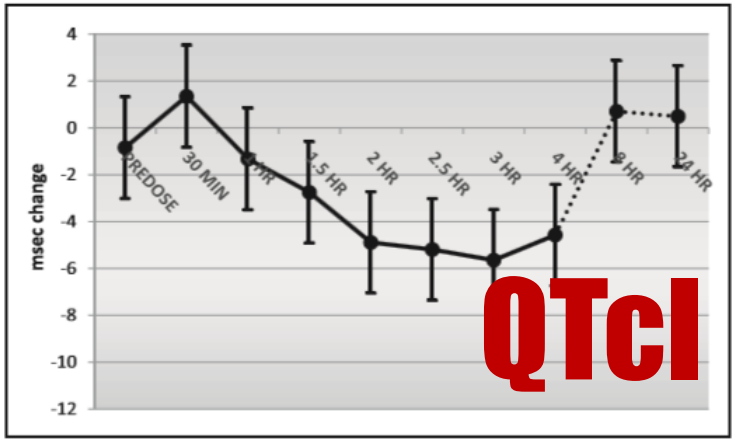
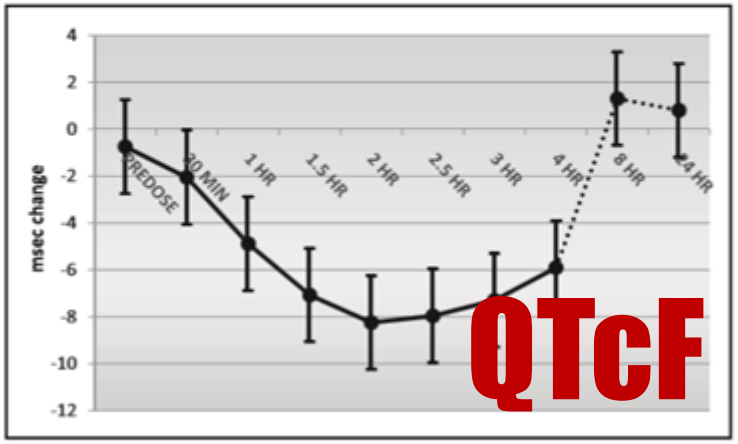


Figure 4. Food effect on QTcIP with confidence interval of 95%.

From: Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies
J Taubel, AH Wong, A Naseem, G Ferber, AJ Camm
The Journal of Clinical Pharmacology 52 (10), 1558-1565

STATISTICAL ANALYSIS

Heart Rate Corrections



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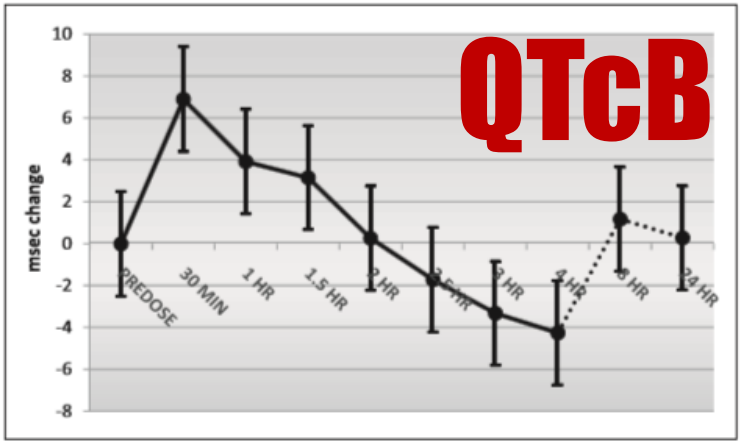
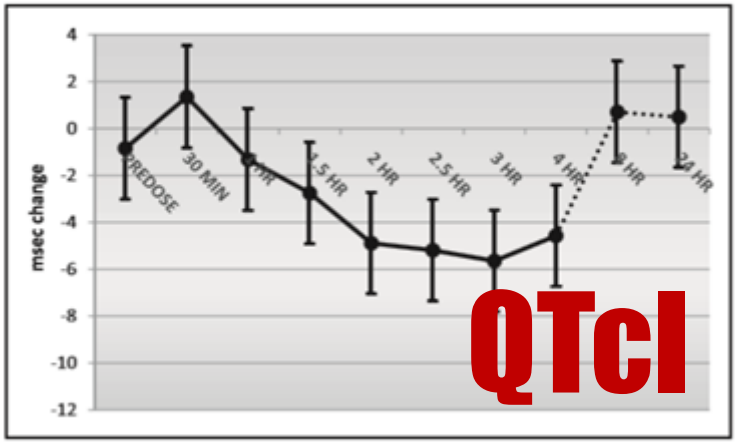


Figure 6. Food effect on QTcB with confidence interval of 95%.



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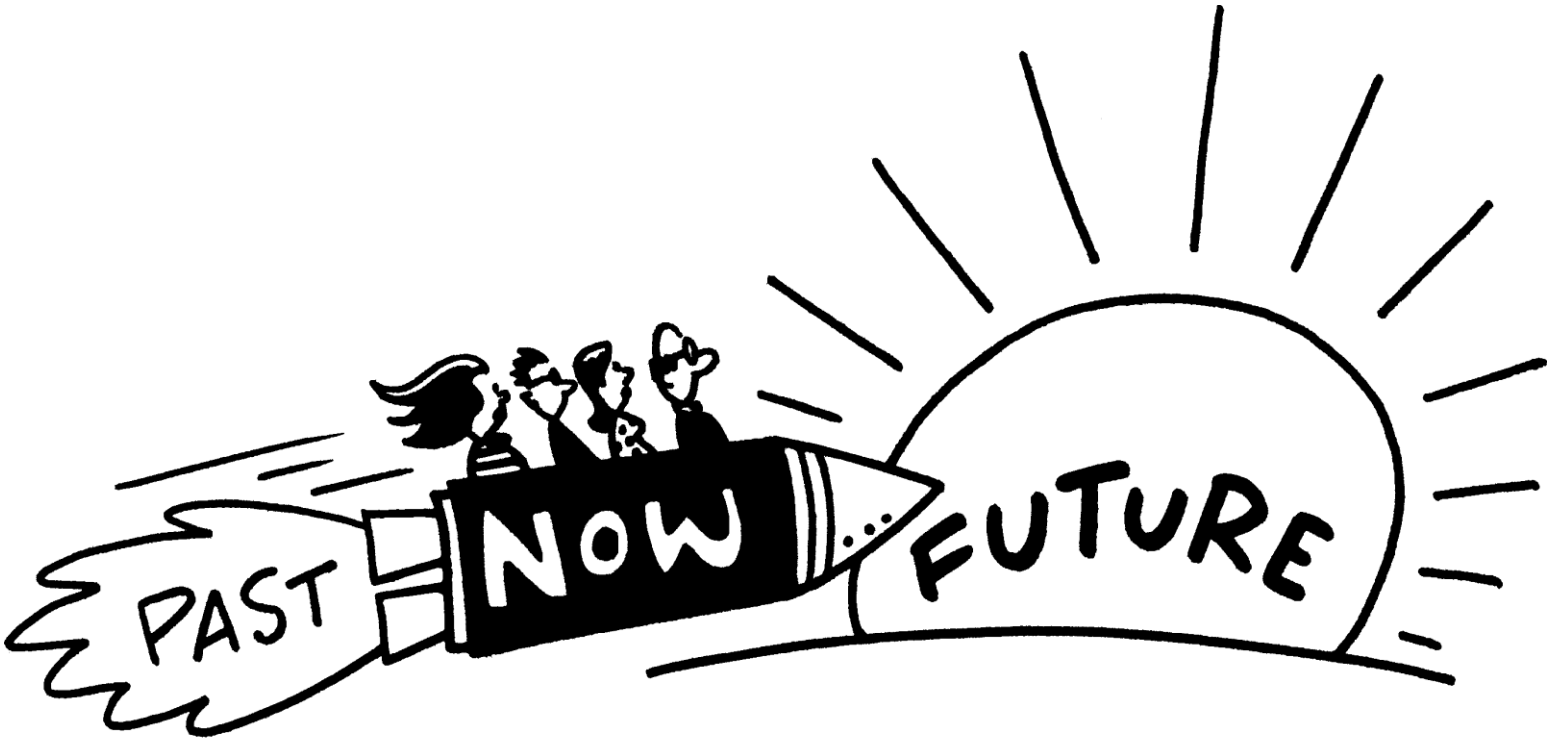
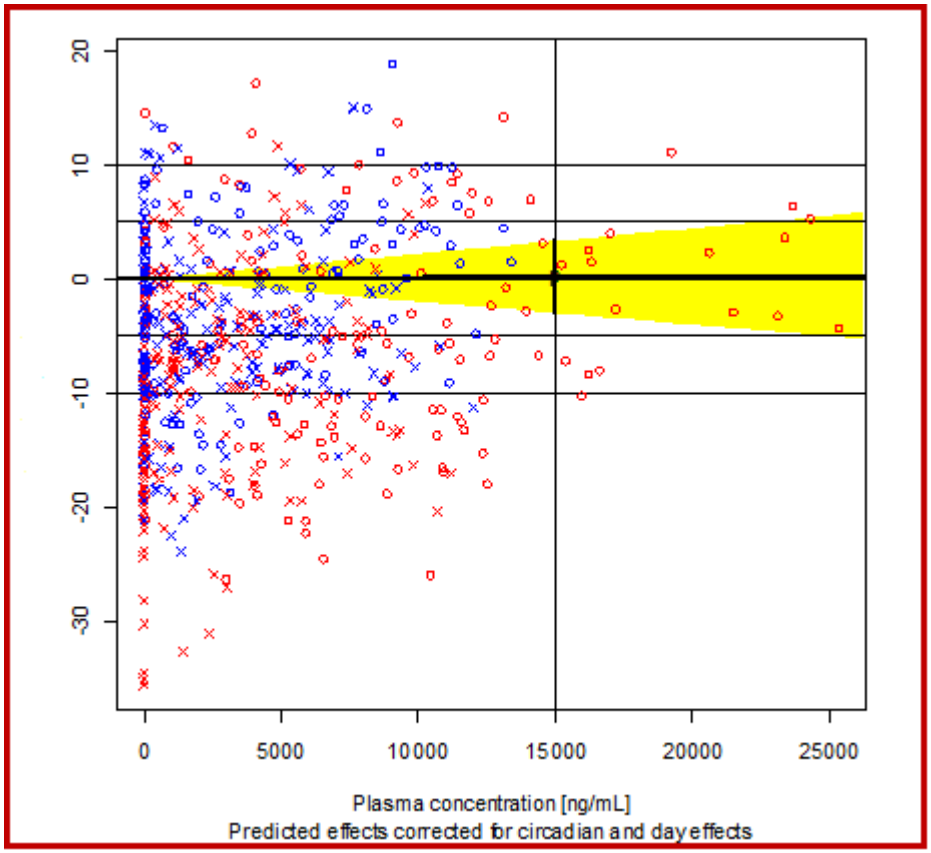


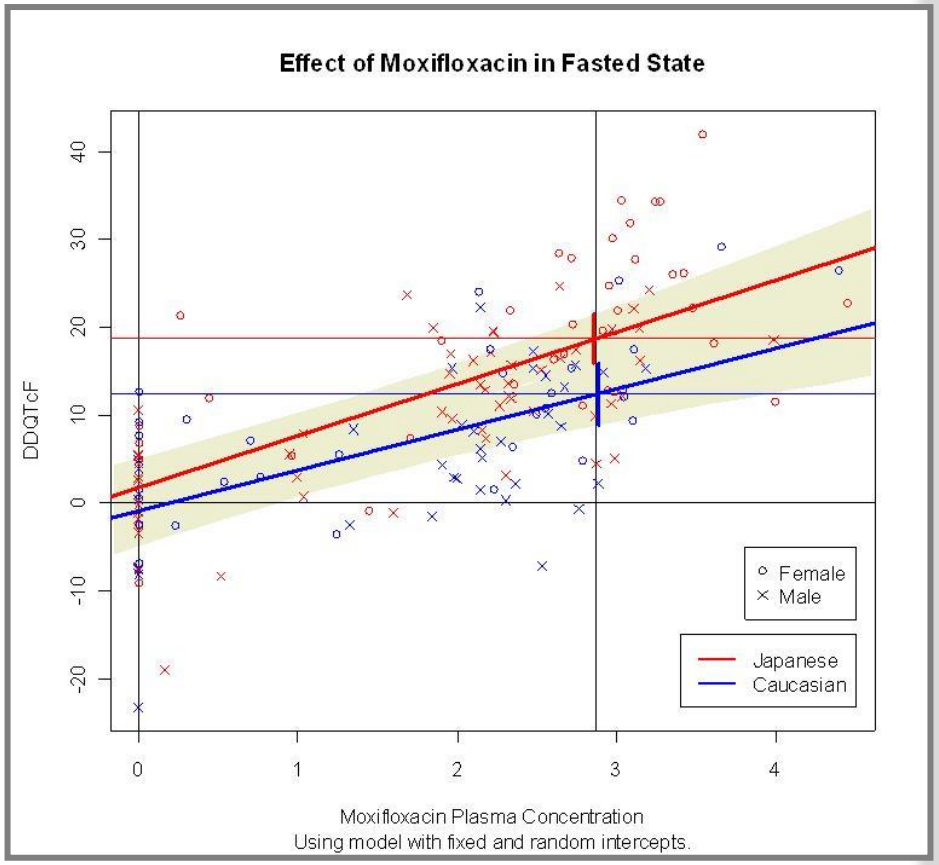
Use of High Quality ECG Data

- From Phase I studies is possible
- Challenges are to assess the data quality
- This is not settled at present.

PK-PD: Recent Case Study



no effect of IMP on the QTc interval



Dose-response relationship

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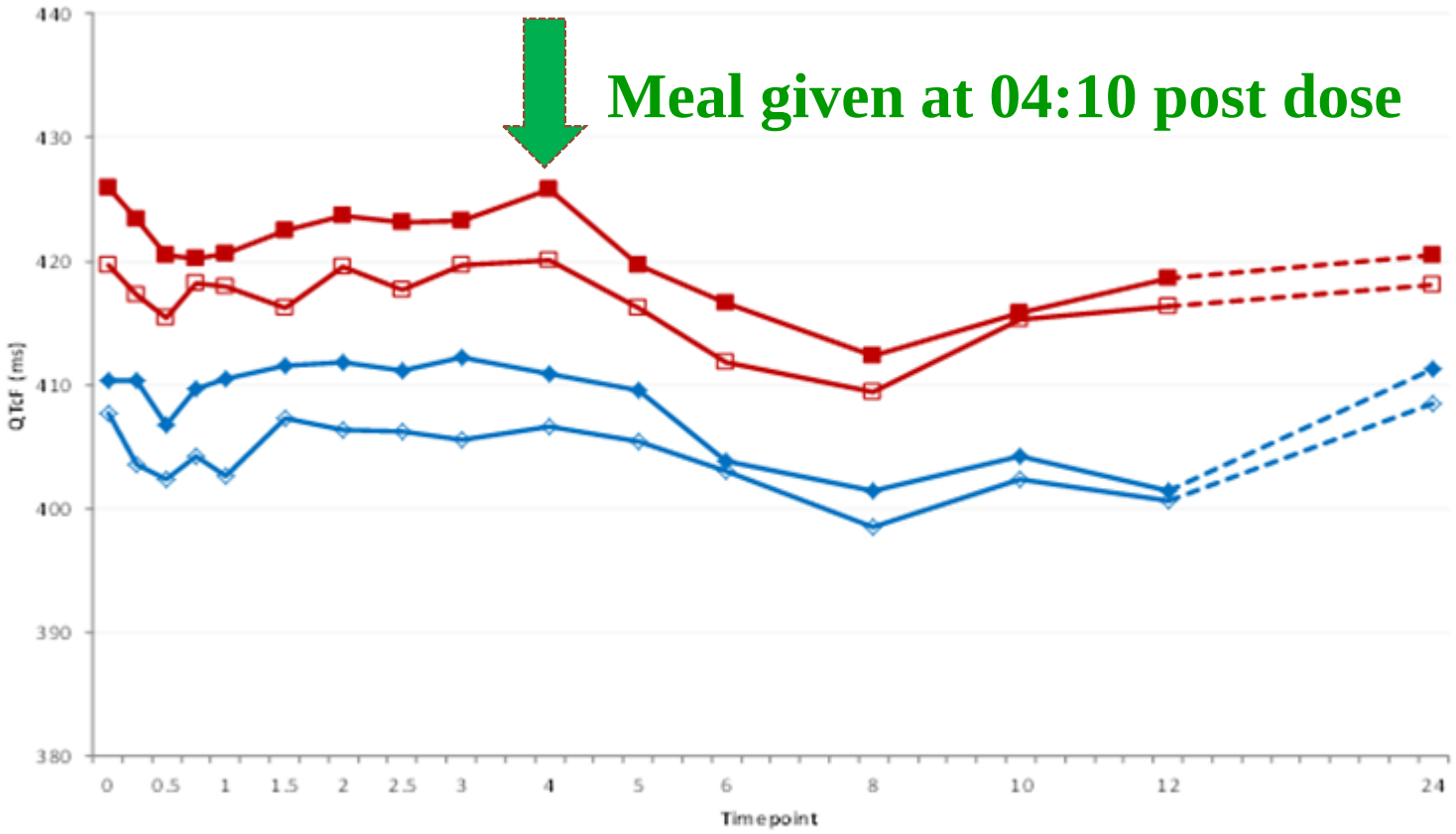
QTcF time course changes



"Radom" or "circadian" effects in this instance represent ***predictable*** and ***reproducible*** changes with a known duration and magnitude.

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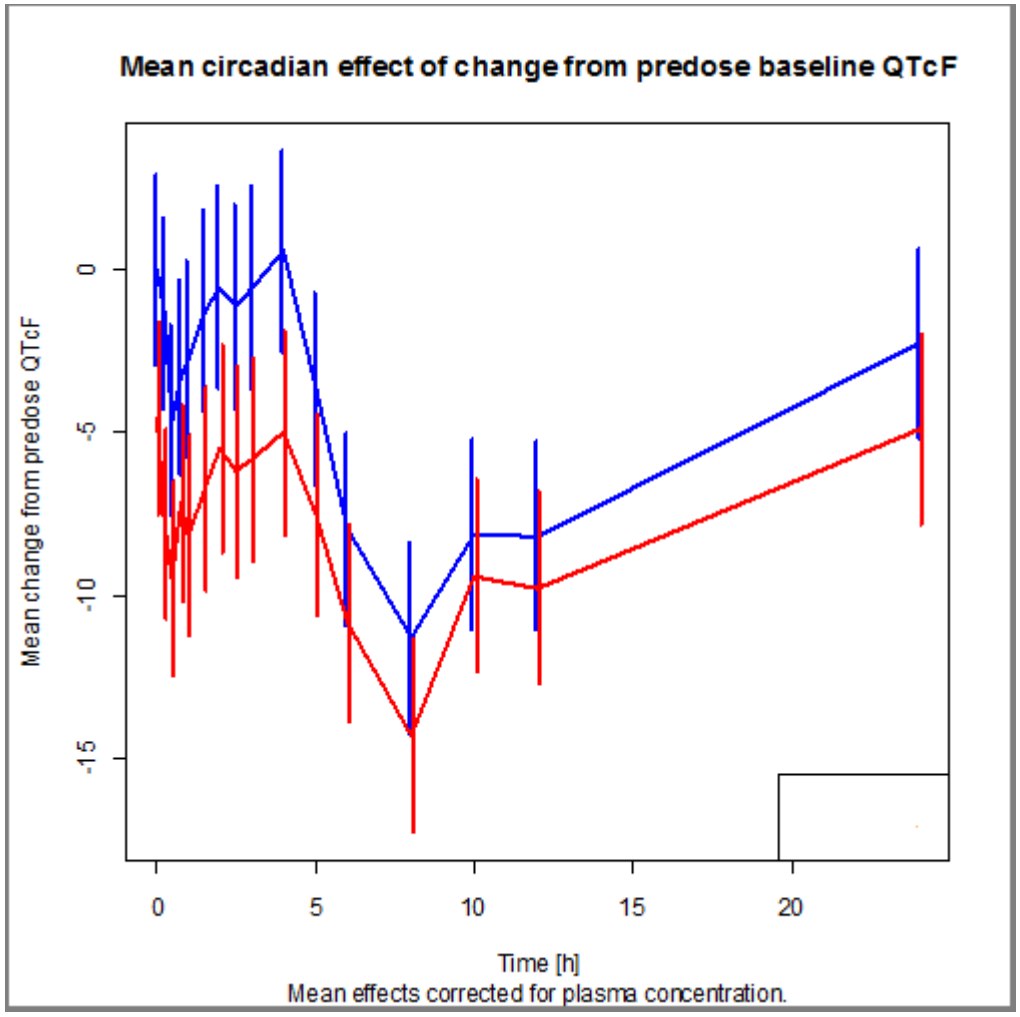
ICH E14 Compliant Validation Tool



A well defined food effect may be used to confirm assay sensitivity:

As the study is sufficiently sensitive to show a food effect it should be deemed to have been adequately sensitive to discover a drug effect if there was one.

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Acknowledgements

- Professor John Camm
- Cardiologists at the Department of Cardiovascular Sciences at St Georges
- Dr Georg Ferber (statistical work)
- Dr Ulrike Lorch (clinical work)
- Clinical team at Richmond Pharmacology

Science. Service. Technology.

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Club Phase 1
Nice, Sophia Antipolis, France
12 & 12 April 2013

Cardiovascular Safety in Oncology Drug Development

Boaz Mendzelevski, MD
Vice President Cardiology

Drug Induced Cardiotoxicity: Contemporary classification

Cardiotoxicity	Key features	Regulatory guidance
Repolarization and Conduction Related Cardiotoxicity	• Assesses risk for drug induced arrhythmia and sudden death • Endpoint Variable – ECG QT/QTc Interval Prolongation; PR and QRS Intervals. • Examples – hERG Blockers - Terfenadine, Cisapride, etc	**ICH-E14 guidance**
Vascular Related Cardiotoxicity	• Assesses Risk for Drug Induced Vascular/Thrombosis Events • Endpoint – MACE: MI, Stroke, Death; Serum Biomarkers, Imaging, ECG • Examples – T2DM drugs (e.g., Rosiglitazone) • COX-2 inhibitors (e.g., Vioxx)	**FDA & EMA Diabetes guidance**
Tissue Related Cardiotoxicity	• Assesses Propensity of NCE to Cause Direct Tissue Damage • Endpoint – HF, Death; Serum Biomarkers, Imaging and ECG • Examples – Oncology Drugs, e.g., Trastuzumab (Herceptin)	**No Guidance (yet)**

Oncology Drug Induced Cardiotoxicity

- **Repolarization Related Cardiotoxicity**
  - **The risk for drug induced arrhythmia and sudden death**
  - **Endpoint Variable – ECG QT/QTc Interval Prolongation**
- **Tissue Related Cardiotoxicity**
  - **The risk of new drugs for causing direct tissue damage**
  - **Endpoint – serum biomarkers, CV imaging and ECG**
- **Vascular Related Cardiotoxicity**
  - **The risk for drug induced vascular/thrombotic events, including changes in BP**
  - **Endpoint – HTN & MACE - ACS, MI, CHF, Stroke, CV Death**

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Cardiovascular Toxicity of Selected Oncology Agents

QTc Prolongation	CHF	Coronary Syndromes	Hypertension
Arsenic trioxide	(Doxorubicin)	(Capecitabine)	Bevacizumab
Depsipeptide	Trastuzumab	Bevacizumab	Sorafenib
VDAs (DMXAA, CA4P)	Lapatinib	Sorafenib	Sunitinib
Sunitinib Dasatinib	Sunitinib	VDAs (CA4P, ZD6126, MN-029)	VDAs
Geldanamycin analogues (17AAG; 17DMAG)	Alemtuzumab		

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Oncology Drug Induced Cardiotoxicity:

QT Prolongation

Chemotherapy Associated QT Prolongation

Chemotherapy Agents	Incidence (%)	Frequency of Use
Histone deacetylase inhibitor		
Vorinostat (Zolinza) (10,131)	3.5–6	+
Miscellaneous		
Arsenic trioxide (Trisenox) (10,163–170)	26–93	+
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	<1–3	++
Lapatinib (Tykerb) (10)	16	+
Nilotinib (Tasigna) (171–173)	1–10	+

Yeh and Bickford JACC 2009:53(24):2231–47

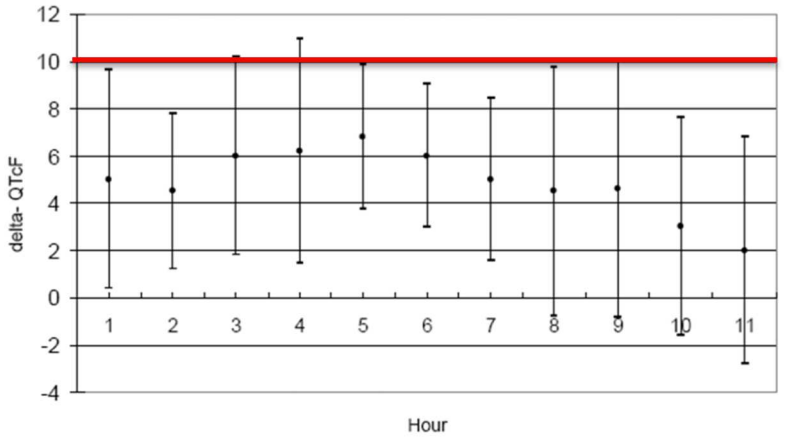
Challenges in Assessing QT in Oncology

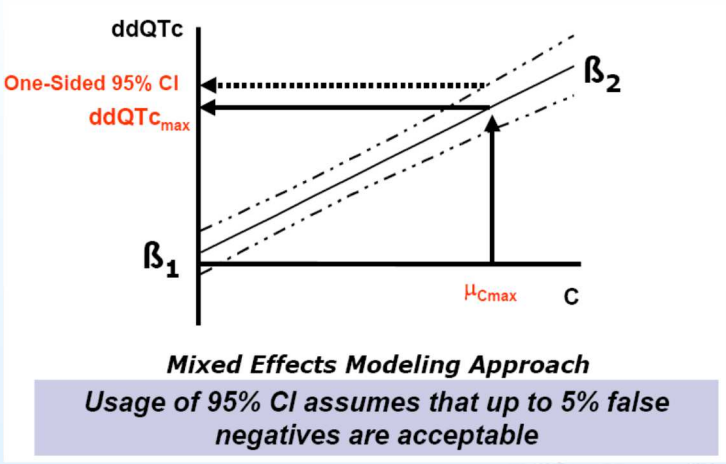
- Genotoxicity and other safety concerns may preclude TQT study of oncology drugs in healthy volunteers
- Target patient population with multiple confounding factors related to disease state, including co-morbidities, concomitant medications, adverse events, electrolyte abnormalities, etc.
- Extended placebo arm not ethically justifiable
- Narrow therapeutic window - testing of supratherapeutic doses (ICH-E14) not safe/ethical

ICH-E14 - TQT Study Considerations

TQT Study Designs:

- Cross-over for drugs with short half life, either with single or multiple dosing
- Parallel design for drugs with long half life, carryover effect, or where as XO is not appropriate
- 4 treatment groups
  - Therapeutic dose
  - Supratherapeutic dose
  - Positive control
  - Placebo
- Typically performed in healthy volunteers, unless risk or tolerability issues prevent this.





Mixed Effects Modeling Approach

Usage of 95% CI assumes that up to 5% false negatives are acceptable

FDA letter (2006)

"At the present time, FDA suggests that for Oncology drugs used in the nonadjuvant setting, a negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 20 ms."

Case Study: Lapatinib (Tykerb)

- Data
  - Advanced cancer patients (N=81) received multiple doses of lapatinib ranging from 175 – 1,800 mg/day
  - ECGs were collected on Day 1 and Day 14
  - Time-matched PK and ECGs collected in 32 patients
- Results
  - 13 of 81 pts had a QTcF>480 ms or a ΔQTcF>60 ms
  - Maximum mean ΔQTcF ranged from 10 - 39 ms with no apparent dose-response relationship
  - Co-administration of CYP3A4 inhibitors, food, and hepatic impairment, result in increased lapatanib exposure and further QT prolongation

Drugs@FDA

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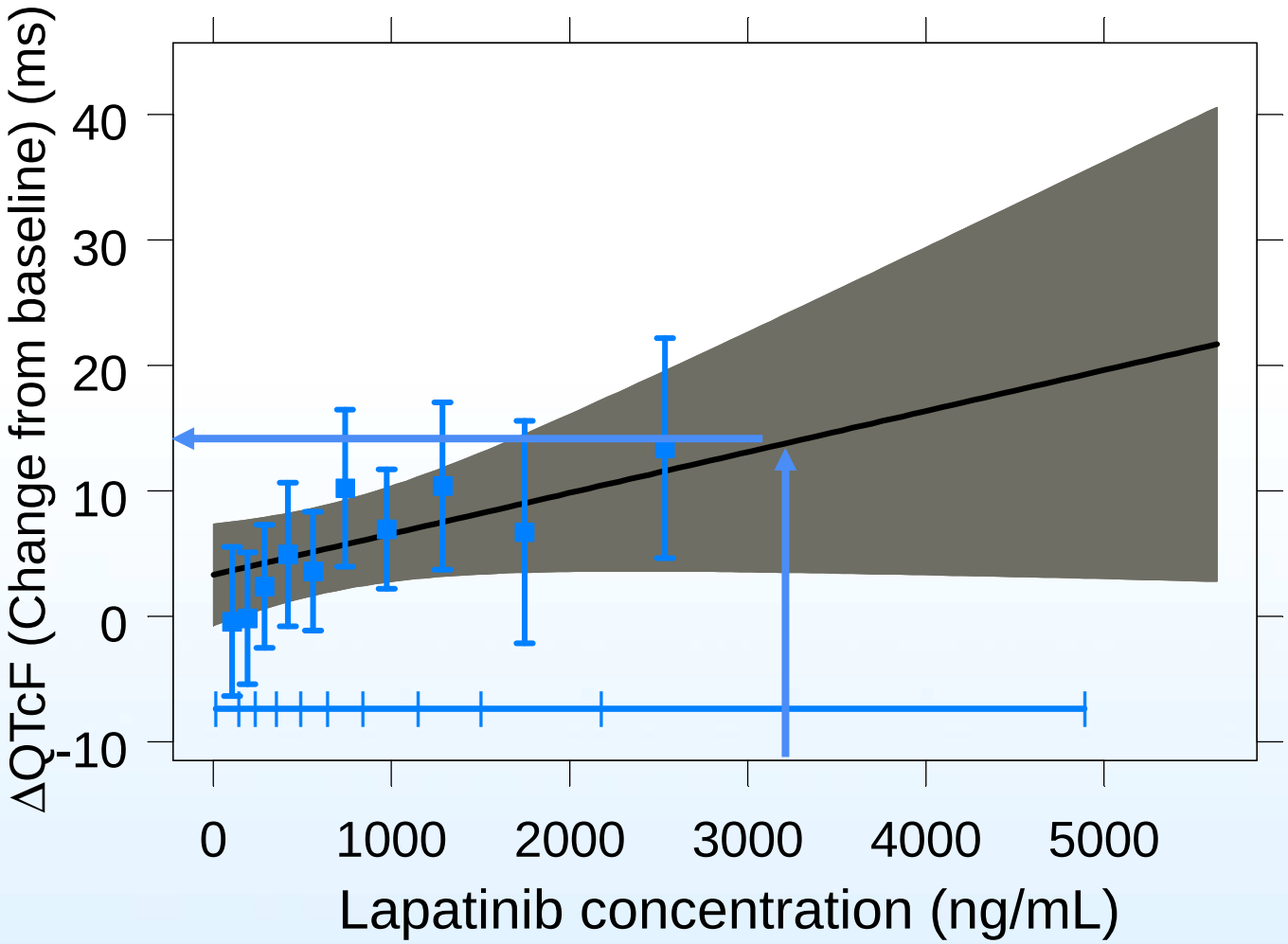
Case Study: Lapatinib (Tykerb) Significant C-E (QTc) Relationship



Case Study: Lapatinib (Tykerb) Label

12.4 QT Prolongation

- The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 mg/day to 1,800 mg/day.
- Serial ECGs were collected on Day 1 and Day 14 to evaluate the effect of lapatinib on QT intervals.
- Thirteen of the 81 subjects were found to have either QTcF (corrected QT by the Fridericia method) >480 msec or an increase in QTcF >60 msec by automated machine-read evaluation of ECG.
- **Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval.**

Drugs@FDA

Oncology Products – FDA Statement

“In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the “TQT” study may be appropriate. Please plan to address this issue early in development.”

Alternative QT Oncology Study

- Start with a typical TQT study design (PG)
- Remove (and justify) aspects as necessary
- Eliminate only processes that cannot be performed, as each omission reduces the “thoroughness” of the study
- Greater reliance on concentration:response modeling for early adaptive QT oncology studies
- MAD studies for modeling; subsequent studies possible for more dedicated evaluations
- More “TQT-like” studies with more indolent cancers QT evaluation expected during oncology development

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Oncology Drug Induced Tissue Related Cardiotoxicity

Chemotherapy Agents/Classes Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++

Yeh and Bickford. JACC 2009:53(24):2231–47

Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

Yeh and Bickford. JACC 2009:53(24):2231–47

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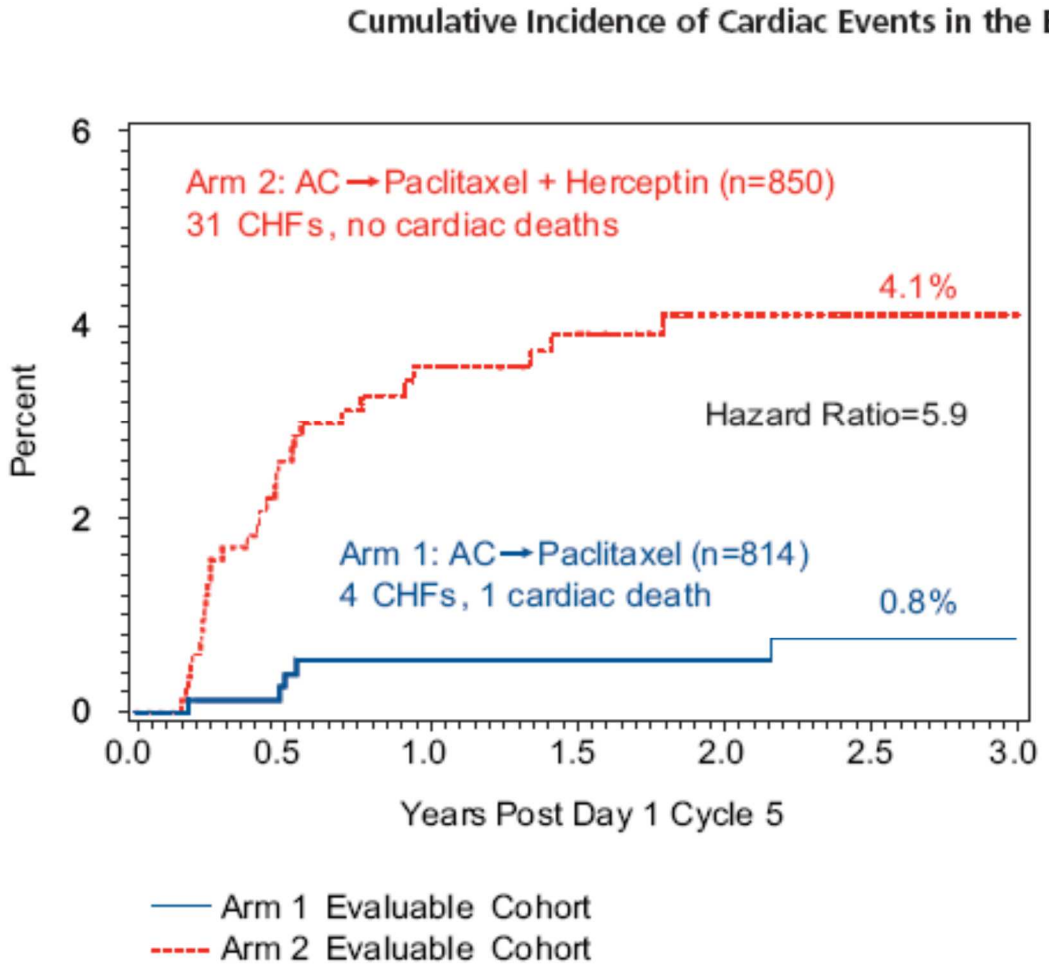
Case Study – Herceptin (Trastuzumab)

- Herceptin (trastuzumab) is a humanized monoclonal antibody targeted against the HER2 protein on cancer cells.
- In 1998, FDA approved Herceptin for the treatment of metastatic breast cancer.
- In 2006 FDA expanded approval to use in women with more localized cancer (only in the breast or lymph nodes which has been removed with surgery).
- Herceptin should only be prescribed for women diagnosed with HER2 positive breast cancer.

Herceptin and The Heart
Results from NSABP study B-31

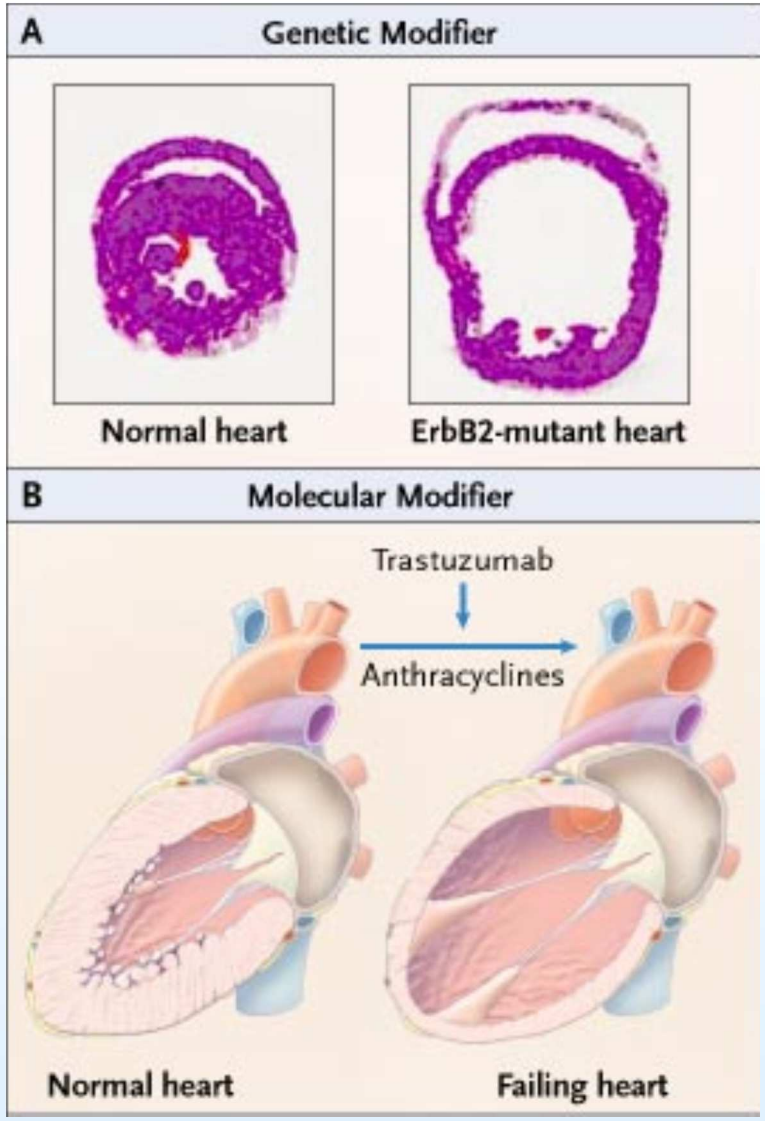
http://www.fda.gov/medwatch/safety/2005/HerceptinDDL_0805.FINAL.pdf



Years Post Day 1 Cycle 5	Cum Inc Arm 1 (%)	Cum Inc Arm 2 (%)	Number at Risk
0.5	0.3	2.6	1466
1.0	0.5	3.6	1200
1.5	0.5	3.9	979
2.0	0.5	4.1	773
2.5	0.8	4.1	593
3.0	0.8	4.1	402

Cycle 5 Day 1 represents the start of paclitaxel or paclitaxel + HERCEPTIN.

Working Model of Trastuzumab as a Molecular Modifier of Anthracycline Cardiotoxicity



NEJM 2006;354:789-790

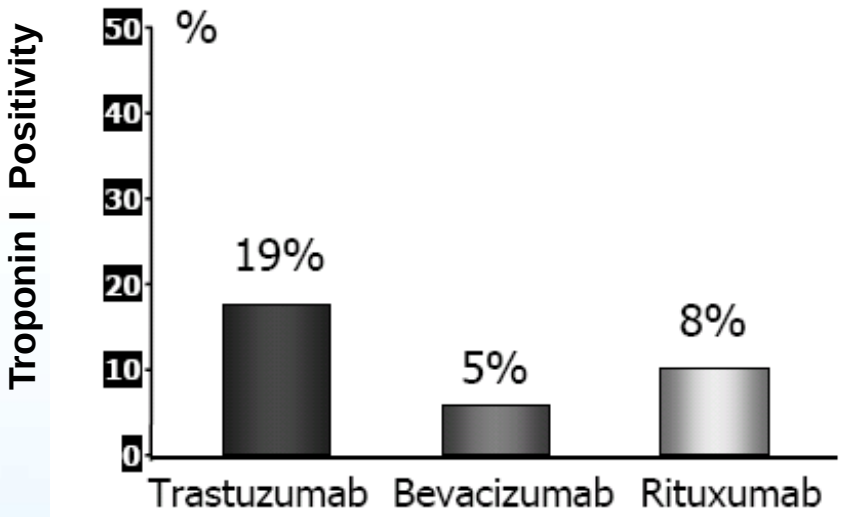
Herceptin Black Box Warning

- **Black Box Warning**
- **WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY**
- **Cardiomyopathy - Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. Infusion Reactions; Pulmonary Toxicity - Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.**

- ***Avoid co-administration with anthracyclines.***

Biomarkers for CV Toxicity

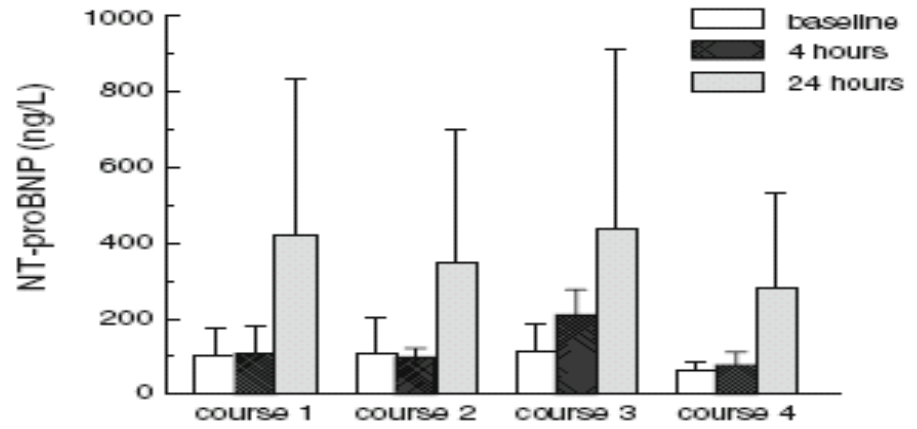
Troponin I



In monoclonal AB Therapy

Daniela Cardinale, MD,
European Institute of Oncology, DIA 2007

NT-pro-BNP



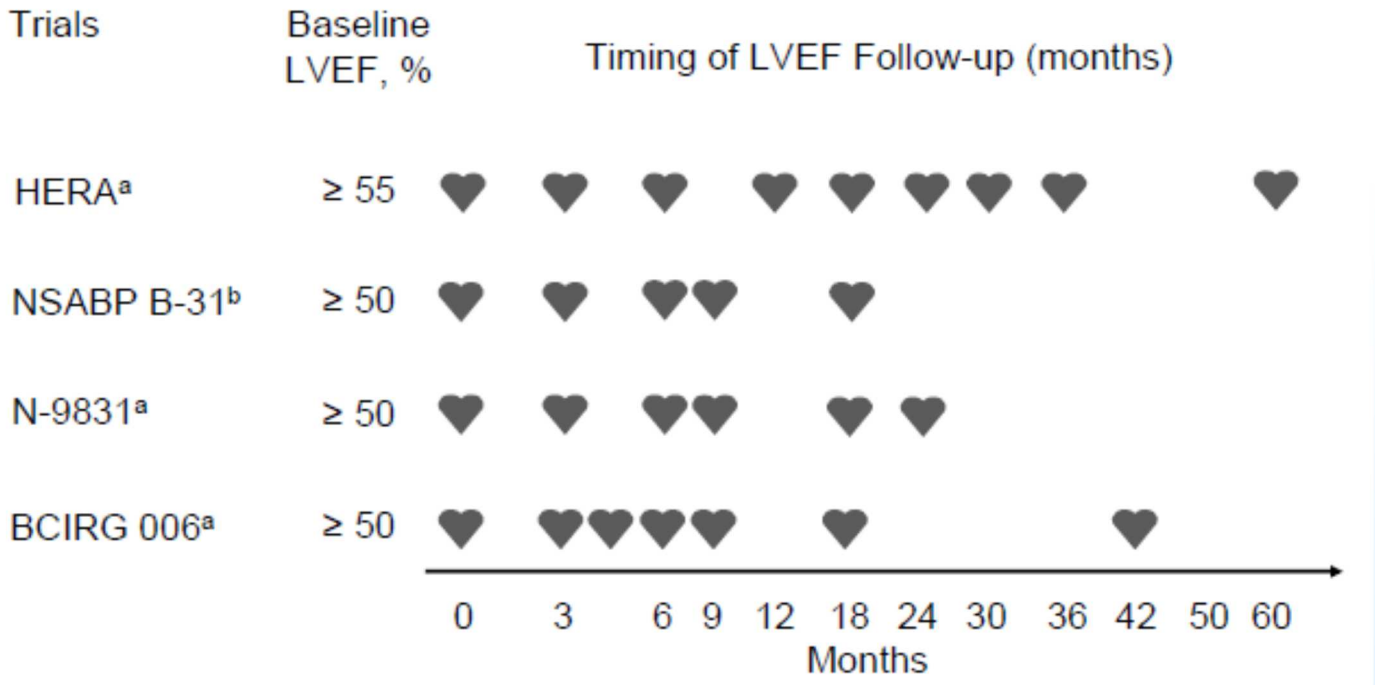
NT-proBNP, mean serum concentration (standard deviation) at baseline, 4 and 24 h in 12 patients who were sampled during each course of anthracyclin-containing chemotherapy

In Anthracycline Therapy

Broeyer et al. J Cancer Res Clin Oncol (2008) 134:961–968.

Imaging biomarkers: Monitoring LVEF in Oncology Clinical Trials

Baseline and Follow-up Cardiac Monitoring (as per adjuvant trials)



[a]MUGA or echocardiography.
[b]MUGA.

Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353:1659-72.
Tan-Chiu, et al. *J Clin Oncol.* 2005;23:7811-9.
Perez EA, et al. *J Clin Oncol.* 2008;26:1231-8.
Slamon D, et al. BCIRG 006 Presentation. SABCS 2009. www.bcirg.org.

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Vascular Related Cardiotoxicity Associated with Oncology Drugs

Chemotherapy Assoc. with Vascular Effects

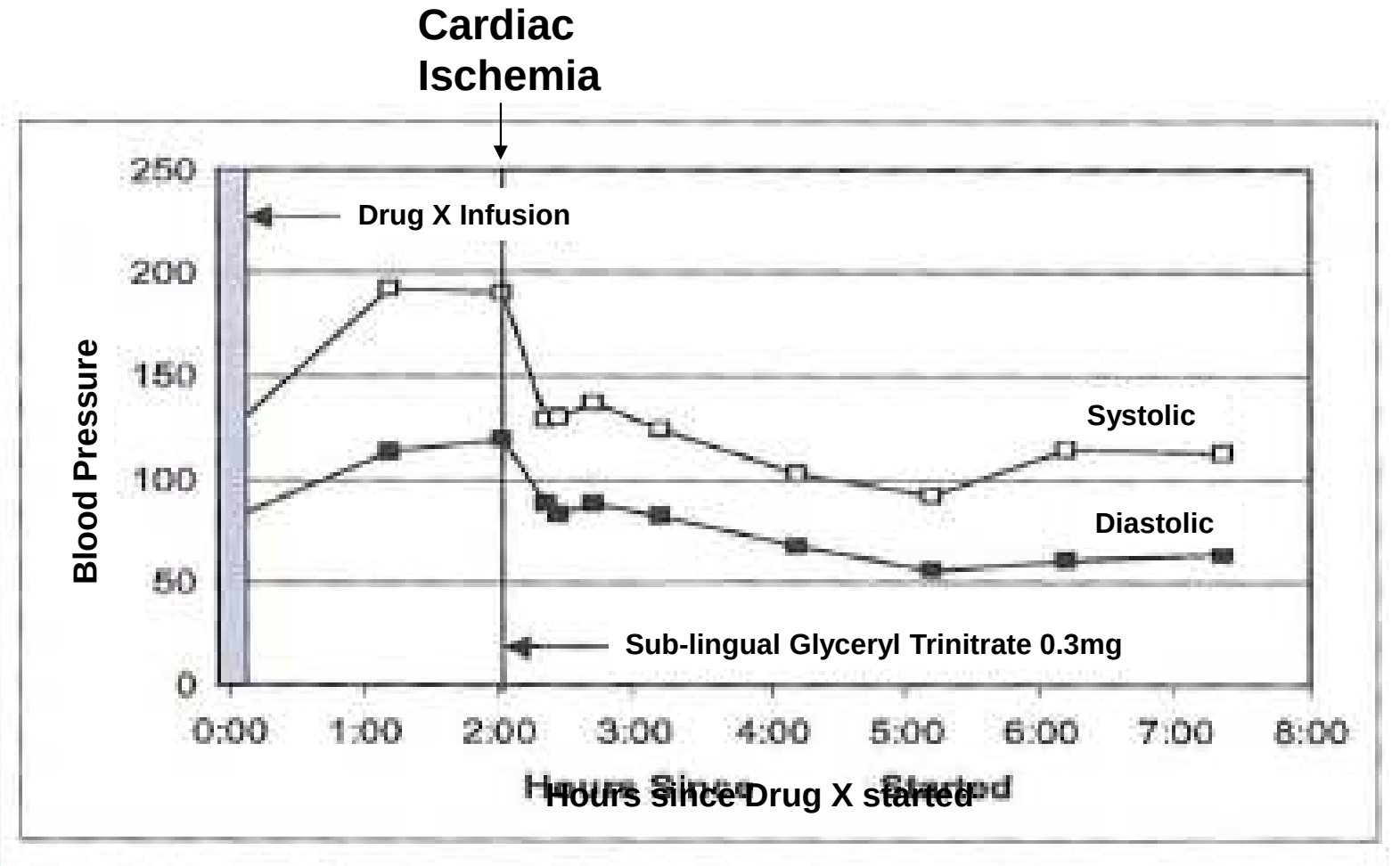
Chemotherapy Agents Associated With Ischemia	Chemotherapy Agents Associated With Thrombo-embolism
Antimetabolites	**Alkylating agents**
Capecitabine (Xeloda)	Cisplatin (Platinol-AQ)
Fluorouracil (Adrucil)	
Antimicrotubule agents	**Angiogenesis inhibitors**
Paclitaxel (Taxol)	Lenalidomide (Revlimid)
Docetaxel (Taxotere)	Thalidomide (Thalomid)
Monoclonal AB - tyrosine kinase inhibitors	**Histone deacetylase inhibitor**
Bevacizumab (Avastin)	Vorinostat (Zolinza)
Small molecule tyrosine kinase inhibitors	**Small molecule tyrosine kinase inhibitors**
Erlotinib (Tarceva)	Erlotinib (Tarceva)
Sorafenib (Nexavar)	

Chemotherapy Induced Hypertension

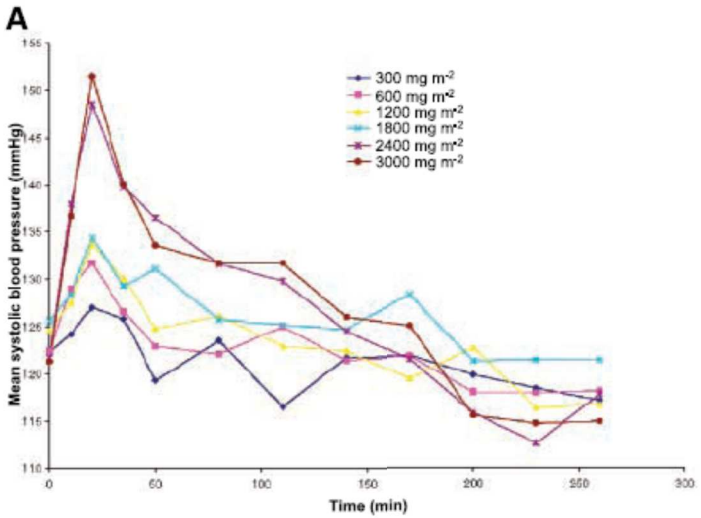
Chemotherapy Agents	Incidence	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin)	4–35	++
Small molecule tyrosine kinase inhibitors		
Sorafenib (Nexavar)	17–43	+++
Sunitinib (Sutent)	5–47	+++

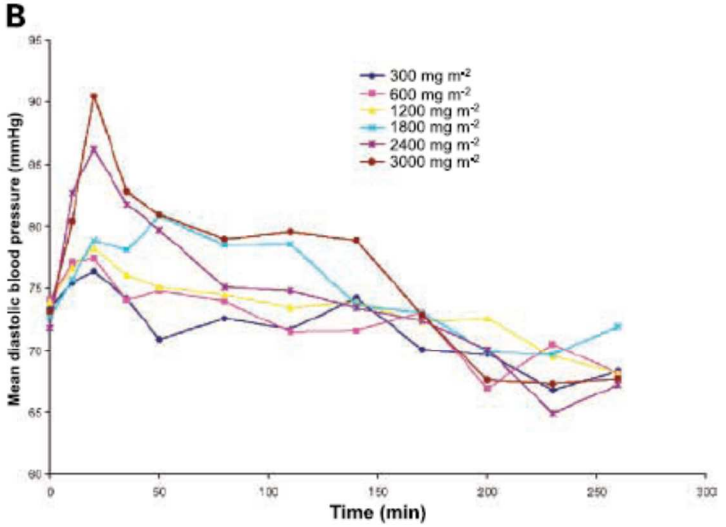
Yeh and Bickford JACC 2009:53(24):2231–47

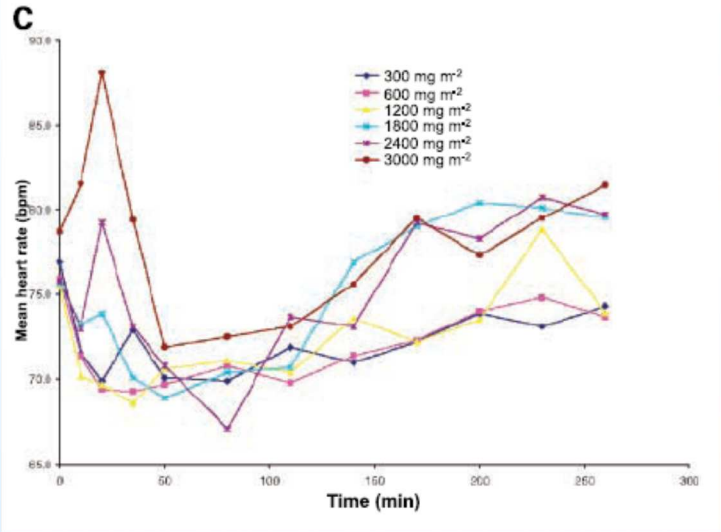
Case A – Investigational VDA



DMXAA Induces Acute Changes in Arterial Blood Pressure and Heart Rate







Clin Cancer Res 2006; 12:1776 –1784

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Summary

Early Detection of Tissue Related Cardiotoxicity

Serum Biomarkers:

- Routine monitoring of serum cardiac biomarkers
  - troponins (HS cTnI)
  - B type natriuretic peptide (BNP)
  - N-terminal pro-B type natriuretic peptide (NT-proBNP)

Imaging Biomarkers:

- Echocardiography (ECHO)
- Multigated Acquisition Scan (MUGA)

ECG monitoring:

- Baseline and on-treatment ECG monitoring (by cycle)

Blood-Pressure monitoring:

- Systematic characterization of BP pharmacodynamics

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Reducing Cardiotoxicity

- Reduce/cease drug administration (?)
- Increase length of infusion (eg, anthracyclines)
- Switch dosage form (eg, anthracyclines)
- Use fewer cardiotoxic agents in combination
  - e.g., docetaxel vs. paclitaxel
- Treat cardiac risk factors
- Treat LV dysfunction
  - ACEI and β-blocker use established in AIC
  - When should pharmacologic treatment be initiated?

Thank You

Questions ?

bmendzelevski@corelabpartners.com