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New Approach to assessing TdP risk without the thorough QT study

Regulatory Risk, uncertainty and implications

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Disclaimer

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The references to the guidelines or papers from the above organisations, are factually represented.

E-14 and Thorough QT study; Achievements;

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- E-14 (& S7B)
  - provided a framework for evaluation of QT liability
  - Defined expectations (for sponsors)
  - Effectively reduced accidental discovery of QT liability of drugs

- Thorough QT study
  - Defined a set of parameters for identifying a risk
  - Provided the regulators and sponsors a decision making tool
  - Perhaps, standardised some of the interpretation and methods of testing

- Disadvantages/ Criticisms---fact of life..

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Overall Risk & Benefit

Drugs approved between 7/2011 to 4/2013

Drug	Indication	CV Risk
Ipilimumab	Melanoma	
Everolimus	Astrocytoma	
Abiraterone	Prostate Ca	QT
Vandetanib	MTC	QT↑↑
Vemurafenib	Melanoma	? QT
6MP	ALL	
Pixantrone	Non-Hodgkin	HF (LVD)
Axitinib	RCC	QT ↑; BP↑
Decitabine	AML (>65yrs)	
Crizotinib	ALK(+) NSCLC	QT↑
Aflibercept	Colorectal Ca	BP↑
Pertuzumab	Her2+ Br Ca	CHF
Bosutinib	CML-Blast phase.	BP ↑; QT ↑

- ~50% of drugs for oncology have QT liability
- the predictability of QT effect is variable (e.g. bosutinib)
- limited QT or torsadogenic risk **is an expectation.**

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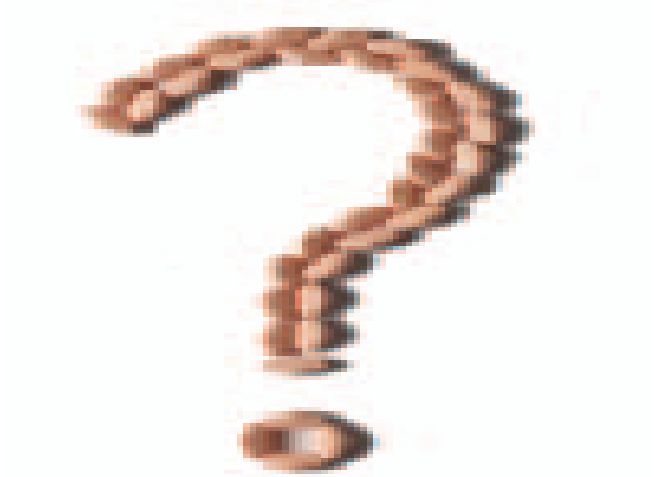
There is Public Expectation…



Will regulators, industry, and the clinical community do a better job for patients next time?

This is a perennial question.....

Pre-clinical evaluations

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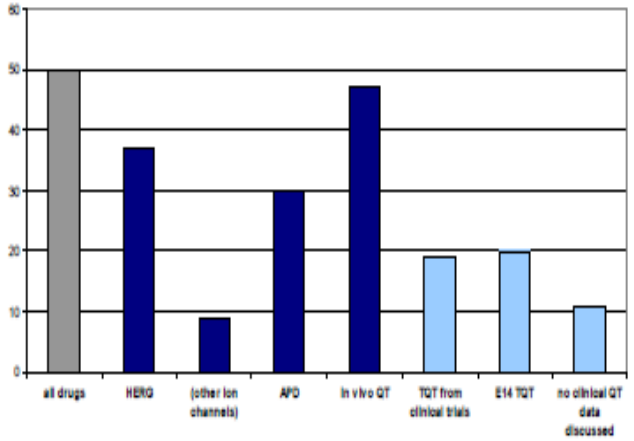
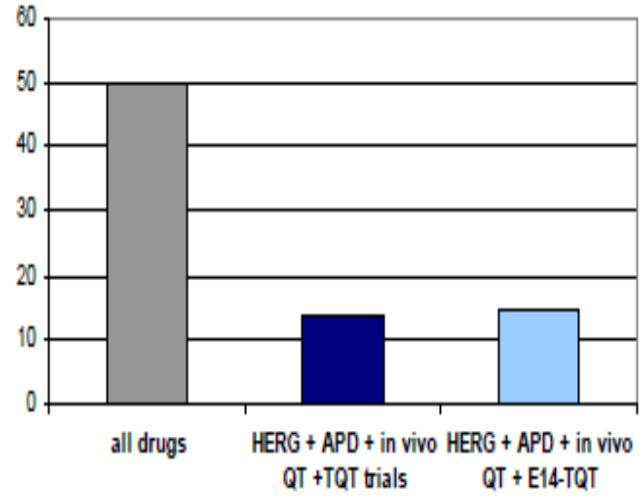
- hERG assay and in vivo studies (S7B)
  - Often the dossiers are non-compliant.
  - hERG trafficking – little information (*Eg; Fluoxetine, Arsenic, petamidine and others*)
- Repolarisation assays: (APD)
  - Limited information in most (APD_{90})
  - Evidence of EADs ?!
- Other indicators of proarrhythmias
  - TDR (transmural dispersion)-limited information

Overall predictability is variable.





Current paradigm:
Models for prediction

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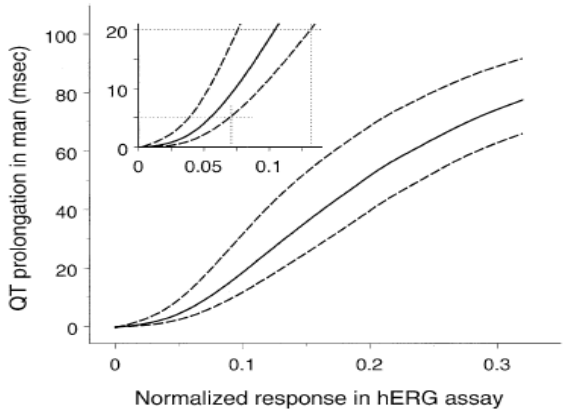

Jonker et al 2005, CPT

Represents a model using **dofetilide** for an individual with baseline QT of 390 ms

hERG	Clinical -	Clinical +
Non-clinical -	10	3
Non-clinical +	0	10

Sensitivity = 77%
Specificity = 100%
Predictive capacity = 87%

In vivo QTc	Clinical -	Clinical +
Non-clinical -	8	2
Non-clinical +	1	10

Sensitivity = 83%
Specificity = 89%
Predictive capacity = 86%

Valentin JP, et al 2009 BJCP

- hERG based
- Relation to dosing and clinical doses needs clarity.
- Metabolite effects? – need better definition

Confounders for pre-clinical data

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For in vitro studies

- Solubility and therefore concentration tested
- Adsorption to surfaces
- Test concentration limited by cytotoxic attributes
- Information on metabolites

In Vivo studies

- Data acquisition & analysis methods- (non-standard)
- Reproducibility of the systems
- Dose, interal and measurement points
- Interspecies differences
- Distinction of Multiple channel effects-

Regulatory risk

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Current paradigm for prediction.

- is a hERG centric approach sufficient??!!
- Need standards for SP study end points translation ➔ to clinical studies
- Evidence of predictive value of SP studies not publicly available consistently.
- Prediction good for QT/QTc but appears dependent on **effect size**

New Paradigm

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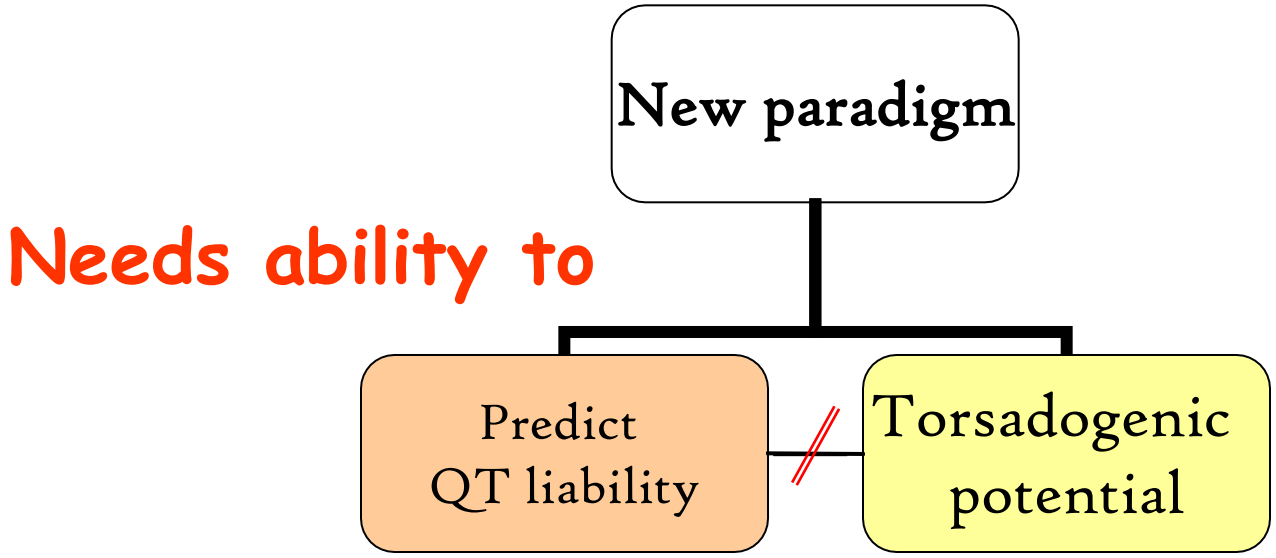

Will require;

Improved predictability and accuracy (sensitivity/ specificity)

Better relation to defining Torsade especially if TQT is not available

Potentials scenarios

(Admittedly rare)

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- (-) NC tests, Phase-I (+) –QT prolongation
- (+) non-clinical test ; phase I –equivocal
- inconsistent NC studies.

However,

In these cases, default position would be to opt for intense monitoring in late phases.

What next?!

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- **In Silico methods**
  - CR data from HTS
  - Medium throughput patch clamps
  - Multi parametric QSAR
  - AP simulation assay

- *Limitations*
  - *Channel specific changes*
  - *Accuracy (Sn/ Sp)*
  - *Variability (with HTS screening)*

- Stem cells;
  - Human cardiac myocytes
  - iPSC –CM
  - iPSCs
  - Undifferentiated hESC

- *Limitations*
  - *Phenotypic consistency?*
  - *Ion channel expressions*
  - *Availability for HTS*
  - *Discrepancy between isolated rabbit hearts & hESC-CM cells in potency.*

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Summary

Current paradigm

- may not be sustainable
- Preclinical tests often non-standardised, and variable.
- Predictability for QT effect but not TdP.

A new paradigm

- or panel will need to address accuracy
- Unequivocal NC and Inconsistency with early phase studies will need to be tackled.

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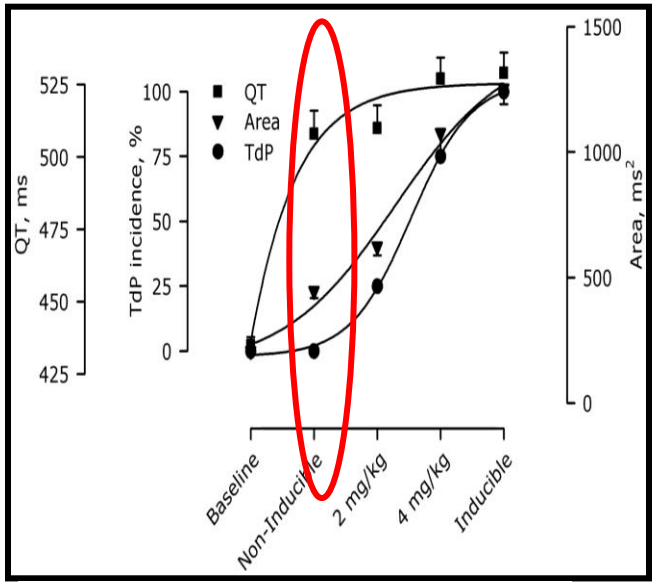
Back Up slides

Limitations of current paradigm (regulatory context)



Thomsen et al. Circulation. 2004; 110:2460-2466

- CV safety evaluation is an inescapable fact
- TQTs burdensome
  - Expense--- ($ x10⁵)
  - Time (delayed development programmes)
- Risk of TdP is elusive
  - QT liability defined but relation to TdP imprecise