

Validation concepts pertaining to the new approach and the tension surrounding risk

B. R. Berridge, DVM, PhD, DACVP
GlaxoSmithKline R&D

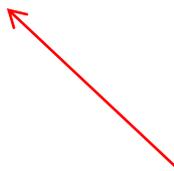
CSRC-HESI-FDA Rechanneling the Current Cardiac Risk Paradigm
FDA White Oak
23 July 2013

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1st disclaimer- I'm not an electrophysiologist



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Introduction

- Our concepts of ‘validation’ are fundamental to our ability to meaningfully develop novel approaches to current CV safety paradigms
- Our concepts of ‘validation’ have slowed our progress in leveraging new knowledge and technologies for more effective and efficient strategies
- We need a serious conversation about what it means to be ‘validated’ and design approaches that enable progress
- I don’t know the right answers!

Introduction

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- Our concepts of ‘validation’ have slowed our progress in leveraging new knowledge and technologies for more effective and efficient strategies
- We need a serious conversation about what it means to be ‘validated’ and design approaches that enable progress
- I don’t know the right answers! ← 2nd disclaimer- I’m not the sharpest tool in the shed!

Considerations

- We need a thorough understanding of the pathobiology we're trying to identify and assess for risk
- We need to gather relevant tools for modeling that pathobiology
- We need to understand the context for how we'll use the information we get from those tools
- We need the guts to take 'calculated' risks and refine our approaches as we accumulate additional learnings



m-w.com

val·id  *adjective* \ˈvɑ-ləd\
A light blue header bar containing the word "val·id" with a speaker icon, the word "adjective" in italics, and the phonetic transcription "\ˈvɑ-ləd\".

Definition of VALID



- 1** : having legal efficacy or force; *especially* : executed with the proper legal authority and formalities <a *valid* contract>
- 2** **a** : well-grounded or justifiable : being at once relevant and meaningful <a *valid* theory>
b : logically correct <a *valid* argument> <*valid* inference>
- 3** : appropriate to the end in view : **EFFECTIVE** <every craft has its own *valid* methods>
- 4** *of a taxon* : conforming to accepted principles of sound biological classification

— **va·lid·i·ty**  *noun*

— **val·id·ly**  *adverb*

 See [valid](#) defined for English-language learners »

See [valid](#) defined for kids »



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[The word 'valid' is highlighted in blue in the original image.]

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 +1  Like

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VALIDATION AND REGULATORY ACCEPTANCE OF TOXICOLOGICAL TEST METHODS

*A Report of the
ad hoc Interagency Coordinating Committee on
the Validation of Alternative Methods*

- The relationship of the test method's endpoint(s) to the biologic effect of interest must be described. Although the relationship may be mechanistic or correlative, tests with biologic relevance to the toxic process being evaluated are preferred.

scientific/biological relevance

- The extent of within-test variability, and the reproducibility of the test within and among laboratories must have been demonstrated. Data must be provided describing the level of intra- and interlaboratory reproducibility and how it varies over time. The degree to which biological variability affects this test reproducibility should be addressed.

analytical performance

- The test method's performance must have been demonstrated using reference chemicals or test agents representative of the types of substances to which the test method will be applied, and should include both known positive and known negative agents. Unless it is hazardous to do so, chemicals or test agents should be tested under code to exclude bias.

**demonstrate performance with
'knowns'**

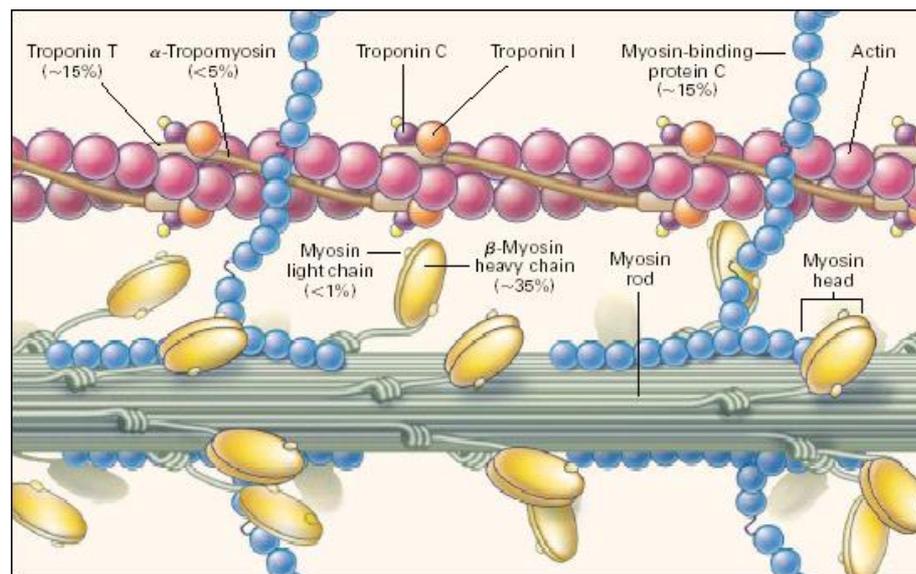
- The limitations of the method must be described; for example, in vitro or other non-animal test methods may not replicate all of the metabolic processes relevant to chemical toxicity that occur in vivo.

understand limitations

Biological relevance of cTns as biomarkers of cardiomyocyte injury

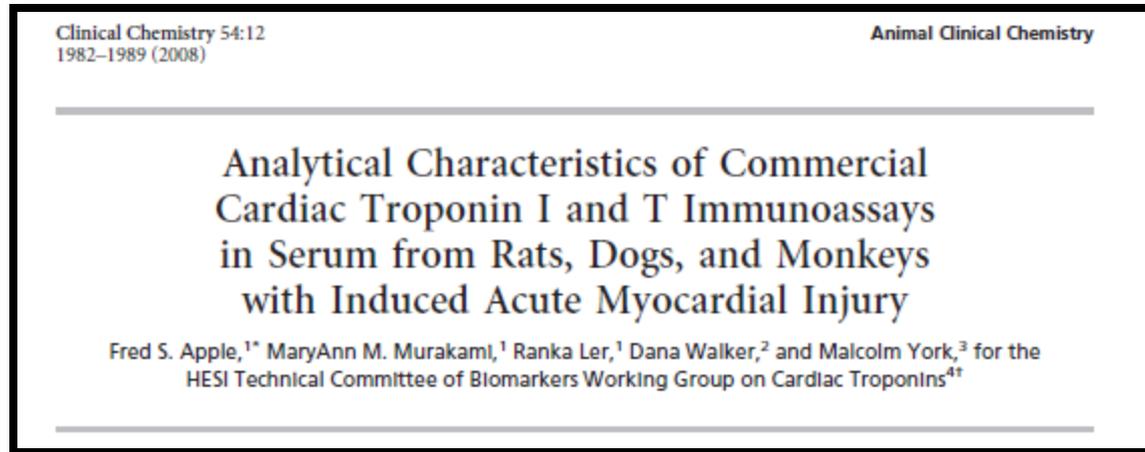
Another place we've had this challenge!

- Protein components of the cardiomyocyte contractile apparatus
- Cardiac and skeletal muscle isoforms (allows specificity for cardiac muscle injury; cf. CK)
- 3 isoforms present in cardiac muscle
 - cTnT- binds tropomyosin
 - cTnC- binds calcium and allows contraction
 - cTnI- inhibits contraction in the absence of calcium
- Low circulating levels of cTn and rapid release with cardiomyocyte injury allow for early detection of injury
- Small cytoplasmic pool (5-10%) but largely linked to structural elements
- Pathogenesis of cardiomyocyte necrosis = fragmentation of the contractile apparatus, breakdown of cell membranes and release of cellular contents into circulation



Spirito et al. NEJM 336:775, 1997

Analytical validation/characterization is the easy part!



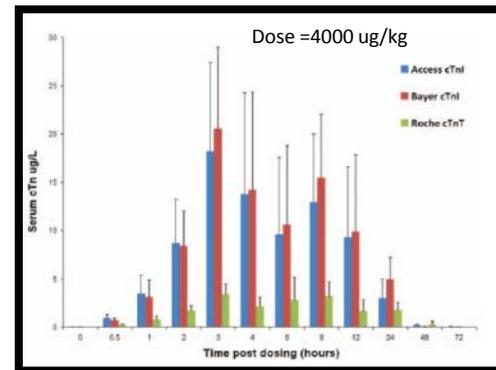
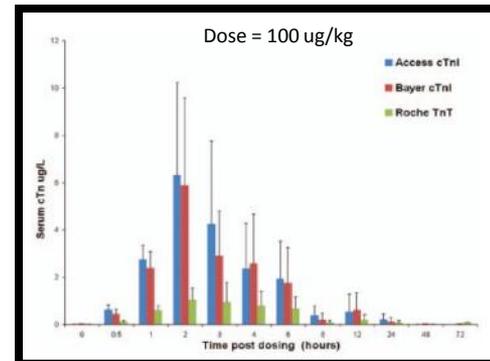
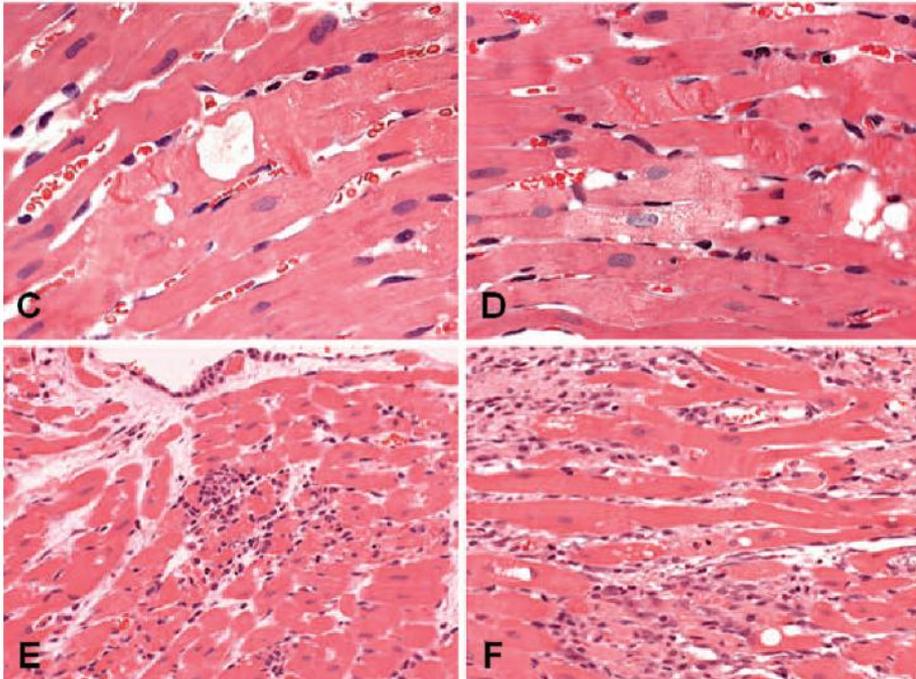
- Sensitivity (LLD)
- Specificity (species)
- Precision/Imprecision
- Accuracy
- CV

This work didn't have anything to do with the relevance of serum cTn as a biomarker of cardiomyocyte injury or the predictivity of cardiotoxicity detected by increased circulating levels of cTn in animals for toxicity in human patients.

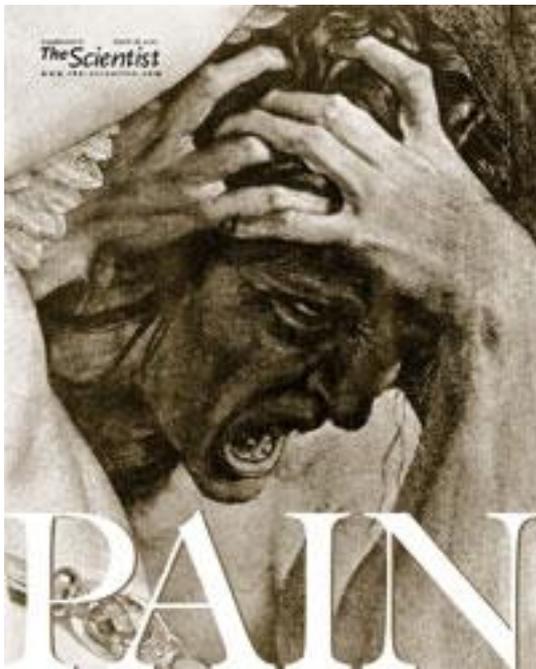
Time Course Characterization of Serum Cardiac Troponins, Heart Fatty Acid-binding Protein, and Morphologic Findings With Isoproterenol-induced Myocardial Injury in the Rat

PETER CLEMENTS¹, SALLY BRADY², MALCOLM YORK¹, BRIAN BERRIDGE³, IGOR MIKAELIAN⁴, ROSEMARY NICKLAUS⁴, MITUL GANDHI¹, IAN ROMAN¹, CLARE STAMP¹, DAI DAVIES⁵, PAUL MCGILL¹, THOMAS WILLIAMS¹, SYRIL PETTIT⁶, DANA WALKER⁸, ILSI HESI CARDIAC TROPONINS WORKING GROUP⁹, AND JOHN TURTON¹⁰

Temporal progression of cardiomyocyte degeneration and necrosis



Temporally progressive and dose-dependent increases in serum cTn



Use of cTn as a translational biomarker of drug-induced cardiac injury has been challenging due to sensitivities associated with it's historic context of use- i.e. ACS and MI

Journal of the American College of Cardiology
© 2000 by the American College of Cardiology and the European Society of Cardiology
Published by Elsevier Science Inc.

Vol. 36, No. 3, 2000
ISSN 0735-1097/00/\$20.00
PII S0735-1097(00)00804-4

Myocardial Infarction Redefined—A Consensus Document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction

The Joint European Society of Cardiology/
American College of Cardiology Committee**

But, experience with application of this marker has refined our understanding of what it tells us- i.e. increased cTn \neq MI

Clinical Chemistry 55:12
2098–2112 (2009)

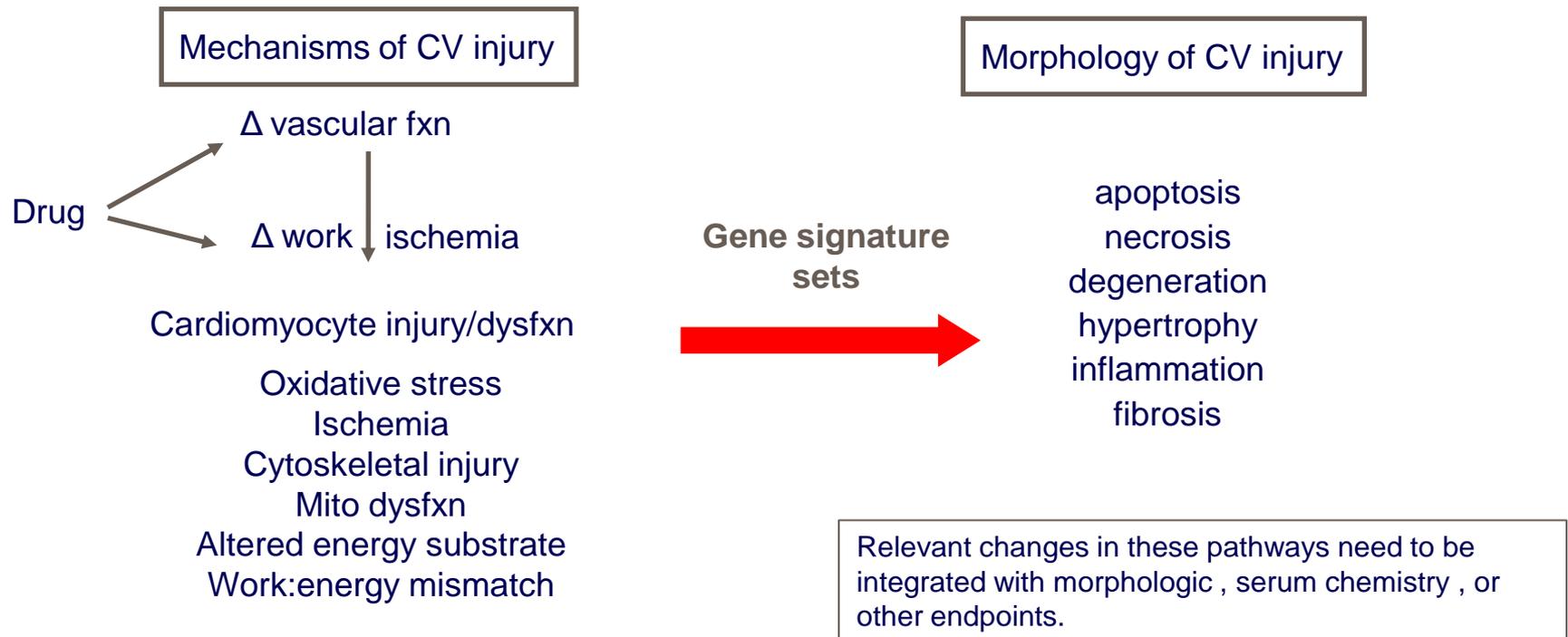
Review

Increases of Cardiac Troponin in Conditions other than Acute Coronary Syndrome and Heart Failure

Walter E. Kelley,^{1*} James L. Januzzi,² and Robert H. Christenson¹

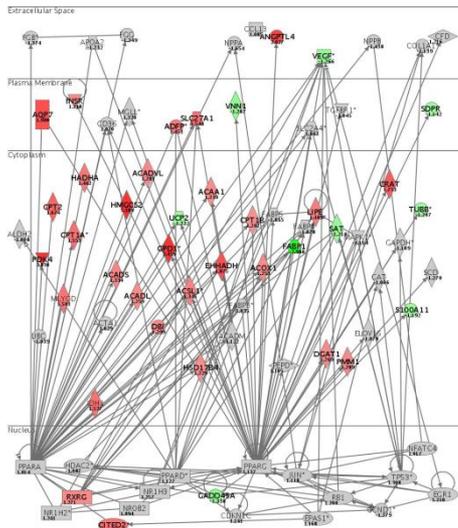
'CardioTaq'- a transcriptomics experience

- Principle = Transcriptional signatures as surrogate for activation of pathologic pathways to provide a “signal” prior to onset of overt cardiac dysfunction or morphologic change.
 - Include key cardiac microRNAs in this approach (tissue biomarker)
- Context of use- short duration tox studies for insights into longer duration liabilities



CardioTaq- defining the ‘signatures’

- Focus on recognized pathologic pathways in the heart- i.e. a supervised interrogation
- Focus on “predictive” signatures
- Fit for purpose study designs for validation of gene sets
- Contextual and translational addition of correlate endpoints



Review

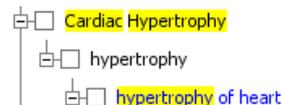
Molecular targets and regulators of cardiac hypertrophy

Rohini Agrawal^{a,*}, Neeraj Agrawal^a, Chintan N. Koyani^a, Randhir Singh^b

Mixed signals in heart failure: cancer rules

Masahiko Hoshijima and Kenneth R. Chien

#	Name	Action	Group	Pathway Category
1	Cardiac Hypertrophy Signaling	View Report Open Pathway	Signaling pathway	Cardiovascular Signaling, Disease-Specific Pathways
2	Role of NFAT in Cardiac Hypertrophy	View Report Open Pathway	Signaling pathway	Cardiovascular Signaling, Disease-Specific Pathways



Ingenuity Pathways/Functions

5,6,7,8-tetrahydrobiopterin, 5-hydroxytryptamine, ACE, ACTC1, ACTG2 (includes EG:72), ADM, ADORA3, ADRB2, AGT, AGTR1, AGTR2, AGTR1B, AHR, AKT1, aldosterone, ANGPT1, ANGPT2, BCL2, beta-estradiol, BMX, CACNA1C, CAMK4, candesartan, carbon monoxide, CASQ2, catecholamine, CAV1, CAV3, CDKN1A, cerivastatin, CNTF, CORIN, corticosterone, CREB1, CRYAB, CTF1, CTNNB1, cyclosporin A, DES, desmopressin, DUSP1, EDN1, EGFR, ELN, EP300, EPAS1, eplerenone, FABP3, FBXO32, FHL2, FKBP1B, flutamide, fulvestrant, GLA,

Integration of Structural and Functional CV Strategies

T2SoC

Early Literature-based Liability ID

SoC2CS

Functional CV cascade

- eXP
- PX ion channel
- Rabbit wedge
- Rat CV

Structural CV cascade

- In vivo pharmacology studies
 - HW, NTproANP, **cTnl**, Histo, CardioTaq*, Echo*
- Pre-CS in vivo rat study
 - HW**, proANP*, **cTnl****, CardioTaq*, Histo**, EM*, Echo*

*selected endpoints added to interrogate putative risks identified in ESP or other investigations

**routinely applied

Preclinical CV Advisory Team (PCAT)

Integrated CV risk assessment
Assess safety margin and risk:benefit

Acceptable

Unacceptable

Off target

Identify probable mechanism of action

Incorporate appropriate assay or screen into LO critical path

On target

One mechanism for mitigating the risk associated with assays or endpoints with which we lack historical context is to include them as components of an integrated strategy that also includes traditional approaches.

Can

GMP P111 studies

CV risk assessment

Cite this: *Toxicol. Res.*, 2012, **1**, 8

www.rsc.org/tx

REVIEW

Validation and quality control of replacement alternatives – current status and future challenges

Marcel Leist, Nina Hasiwa, Mardas Daneshian and Thomas Hartung

Validation approaches

- Correlative approach
 - Input-output system
 - Black box models
 - E.g. rodent carcinogenesis
 - Exceptions learned with experience
- Re-constructive approach
 - 're-construct' reality
 - Biological information + mathematical relationships
 - Requires an understanding of the biological process to be modeled
 - E.g. PBPK modeling
- Whose the 'gold standard'?



Validation of an *in vitro* contractility assay using canine ventricular myocytes

A.R. Harmer*, N. Abi-Gerges, M.J. Morton, G.F. Pullen, J.P. Valentin, C.E. Pollard

- In vitro dog ventricular cardiomyocyte substrate
- Electrical pacing
- Optical quantitation of sarcomere shortening
- Positive and negative inotropic standards
 - outcomes linked to historical experience in either dog or humans
- Traditional sensitivity/specificity grid established
- Significant mechanistic limitations justified by context of use and throughput

Need for and feasibility of a comprehensive non-clinical assay for the pro-arrhythmic potential of new drugs

D Abernethy¹, AM Brown², T Colatsky¹, C Garnett³, G Gintant⁴, CT January⁵, L Johannesen¹, J Koerner¹, J Kramer², N Kruhlak¹, D Leishman⁶, M Malik⁷, S Polak⁸, P Sager⁹, N Stockbridge¹, D Strauss¹, N Thomas¹⁰, J Zhang¹⁰

¹Food and Drug Administration; ²ChanTest ; ³Certara; ⁴AbbVie; ⁵University of Wisconsin; ⁶Eli Lilly; ⁷St. Paul's Hospital; ⁸SimCyp; ⁹Independent Consultant; ¹⁰GE

- “While TdP is associated with prolongation of the heart rate corrected QT (QTc) interval on the ECG and QTc prolongation is highly sensitive to drugs and other conditions, it is a poorly specific marker for the development of TdP.” (Gap analysis)
- “TdP is triggered by early afterdepolarizations and the proclivity of cardiac myocytes to undergo depolarization during the repolarization phase of the action potential, plus heterogeneity of repolarization.” (Understanding of the pathobiology)

Need for and feasibility of a comprehensive non-clinical assay for the pro-arrhythmic potential of new drugs

- “We have asked whether one might be able to define a new paradigm that uses high-throughput methods to develop a more comprehensive picture of a drug’s direct proarrhythmic potential, reducing false positive conclusions that exclude safe drugs from development, through a more nuanced understanding of drug effects on ion channels of cardiac myocytes, while maintaining the presently achieved low rate of false negative safety evaluations.” (Tools are available)
- “We also recognize that employment of a more permissive paradigm may result in development and approval of drugs whose true potential for pro-arrhythmic risk is not evident until post-marketing. We assert our belief that a more comprehensive assessment of proarrhythmic risk will stimulate development of new and useful drugs, a societal impact greater than that of the risk of rare product removal for severe but very rare side effects.” (Risk:benefit is biased toward benefit)

We may be too focused on ‘prediction’!

- “Prediction is very difficult, especially if it’s about the future.” Niels Bohr
- “The only relevant test of the validity of a hypothesis is comparison of prediction with experience.” Milton Friedman
- “A perfect preclinical assay or testing strategy would be 100% predictive for a clinical outcome in all patients. That assay doesn’t exist.” Brian Berridge
- Maybe the goal should be ‘informed progression’ where putative liabilities are recognized and managed in the context of the clinical target.
- We have a fair bit of experience doing this job, a depth of understanding in some areas of risk, and relevant tools. We should apply this collective to the maximum benefit of the patients we seek to serve taking calculated risks.