Is the Current Non-Clinical Drug Development Safety Paradigm Effective for Assessing Cardiovascular Liabilities?

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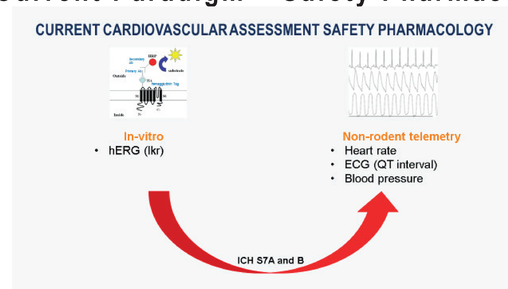
1 Position Statement

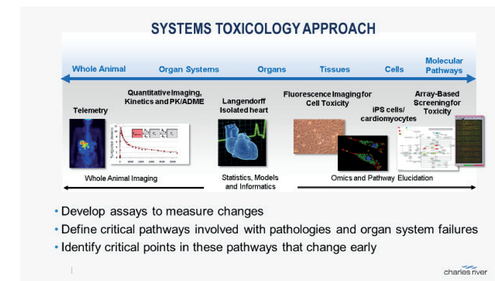
The primary cause of drug removal from development has oscillated between hepatotoxicity and cardiotoxicity, however cardiotoxicity has consistently moved to the top of the list over the last two decades. Cardiovascular adverse events, referenced in a summary by Valentin and Redfern (SOT 2017), describes the following: post marketing (49%), registration (36%), Phase I-III (35%) and non-clinical (27%) as the development stages with the highest percentage of adverse events/failures. What are we "missing" during the nonclinical development phase? Are the assays relevant? Do the functional endpoints translate to the clinic? How much of a change in a cardiovascular functional endpoint measured in a nonclinical model is meaningful to the clinic? These questions are currently being debated by the world's best drug development experts. The comprehensive in-vitro proarrhythmia assay (CiPA) is a current schema that is under development to provide a nonclinical assay for the potential of a drug to develop an arrhythmia compared to the current ICH S7B guidance for assessing compounds against blocking the hERG cardiac ion channel. It is known, that since the advent of ICH S7B in 2005, no drugs have been withdrawn for development of Torsades de Pointes. So, the overarching theme of the CiPA program is to bring forward drugs that do not possess properties for arrhythmogenicity. Something the current guidance cannot state with assessing hERG alone. However, drug attrition is still greater than 30% in most stages of development for cardiovascular adverse events. CiPA addresses only a limited area of potential drivers for cardiac toxicity. Could it be that the heart's ability to function properly, specifically, the ability to contract and relax appropriately for each beat would require additional attention? And if CiPA is exponentially better than the current paradigm for screening compounds against the ability to generate an arrhythmia, wouldn't that mean that even more drugs, some with cardiovascular liabilities other than those that affect ion channels, have the potential to advance in development? This poster describes an integrated cardiovascular de-risking paradigm with a focus on assays, test systems, end points and biomarkers of interest with translation from single cell to whole animal and from acute to chronic study designs.

2 Current Paradigm – Safety Pharmacology



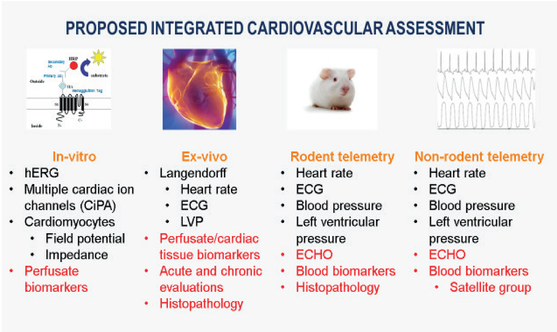
The current paradigm, based on ICH S7A and B, for cardiovascular safety pharmacology requires that drugs in development be assessed against the potential to block hERG and to prolong the QT (QTc) interval of the ECG of a non-rodent species, along with assessing heart rate and blood pressure.

3 Systems Toxicology Approach



A systems biology approach would be a potential contrast to the current processes of how assays utilize advanced technologies to assess endpoints (functional, structural or biochemical) that are affected by test articles. Specifically, designing assays from single cell through whole animal and utilizing tools to assessing the pathways that may be critical in the developed phenotype (e.g., ECG changes, contractility, etc.). By identifying the critical (predictive and/or translatable) pathways (endpoints) within the system that change would allow for these tools to be applied earlier in the drug development process where modulation of the compound can occur to screen out the liability and/or early go/no go decision making can occur.

4 Proposed Paradigm – Integrated Approach



In the proposed, integrated, paradigm, the cardiovascular system could be assessed from in-vitro (single cell, ion channel and/or cardiomyocyte), to whole heart, to telemetered guinea pig (or rat if only hemodynamic endpoints are of interest) and finally large animal telemetry. Each assay offering more complexity with specific functional endpoints of interest, options for additional endpoints and biomarkers to interrogate the system. This paradigm, although designed with options for more complex assays or integrated systems, can be entered at any point with direction of progression based on objectives.

5 Biomarkers

MYOCARDIAL DYSFUNCTION – HEMODYNAMIC STRESS

- Stretch response and "hard work", volume overload (heart failure)
- ➢ Pro-B-type natriuretic peptide
- ➢ NT-proBNP (inactive form)
  - Associated with left ventricular dysfunction
- ➢ Atrial natriuretic peptide
- ➢ Myoblobin (non-specific), combine assessment with cTn
  - Induce diuresis and vasodilation (multifactorial)

- Stretch response and pressure overload – diastolic dysfunction
- ➢ Galectin-3
  - Secreted by macrophages, reacts to inflammation, fibrosis and remodeling
  - Correlates with left ventricular diastolic dysfunction (dog)

CORONARY VASCULAR INFLAMMATION

- ➢ Hs-CRP – indicative of future myocardial infarction, part of risk assessment
  - Acute phase reactants
  - Increases with inflammation (MI and trauma)
- ➢ IL-6 - proinflammatory
- ➢ TNF-α – proinflammatory, effects on inotropy
- ➢ IL-1 – proinflammatory
- ➢ hFABP – oxidative stress within the vascular wall

- Diastolic dysfunction
- ➢ SERCA down regulation
  - Galectin-3 – future advantages in preclinical studies?
- ➢ Heart rate, dP/dt_{max}, dP/dt_{min}, end diastolic pressure
  - Calcium (kinetics)
  - Echocardiography

MYOCARDIAL CELL DAMAGE AND ISCHEMIA

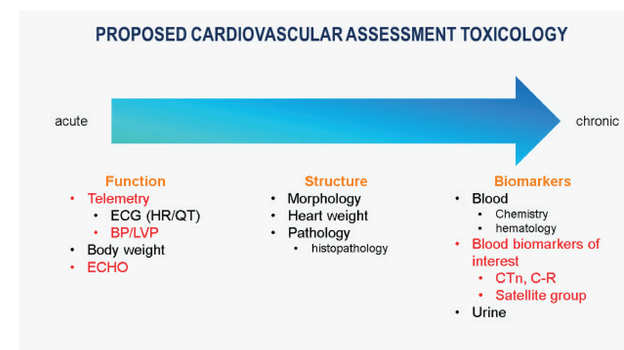
- ➢ Cardiac troponins
  - Hs-cTnI
  - Hs-cTnT

- ❖ Time course
- ❖ 4 – 8 hours (cytosolic)
- ❖ Peak 10 – 24 hours (structural)
- ❖ Decays over 10 – 14 days

- Systolic (contraction) and Diastolic (relaxation) dysfunction
  - heart rate, dP/dt_{max}, blood pressure, and oxygen supply/demand
    - Calcium (kinetics)
  - Echocardiography

Biomarkers (blood, protein and perfusate) are critical data points to include with cardiac functional and structural measurements. Myocardial dysfunction through hemodynamic stress, resulting from sustained elevations in heart rate and/or blood flow, results in the release of enzymes in an attempt to restore normal circulatory conditions. Coronary vascular inflammation is a biological response to damaged cells that produces a protective response leading to and stimulating cardiac remodelling and fibrosis. Myocardial cell damage may result progressively from cell membrane leakage to necrosis, which may result in early detection of cytosolic cardiac troponins to cardiac troponin complexes being detected in the blood or perfusate.

6 Cardiovascular Assessment - Toxicology



This process can further supply information for the repeat dose toxicology studies with regard to cardiovascular functional endpoints and biomarkers. Applying these concepts while investigating the cardiovascular system in repeat dose toxicology studies may provide the data to support utilizing implanted telemetry with left ventricular pressure capabilities vs snap shot ECG collection, as well as, provide the timing of when to sample the blood or tissue for the presence or absence of biomarkers. Lastly, utilizing imaging modalities as clinical translational tools can provide real-time progression of effects related to cardiac structural changes.