CSRC/FDA Blood Pressure Thinktank Meeting 2012: Current Animal Models & Preliminary Performance Assessment

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Preclinical Blood Pressure Evaluation

Assay expectations *differ* with drug discovery stage

Early Discovery: Hazard Identification (early "de-risking")

- screening for effects (heart rate, blood pressure, ECG, contractility)
- *in vitro* preparations (e.g. aortic rings), pharmacological profiling (receptor binding) and *in vivo* studies (typically smaller mammals)

Late Discovery: Risk Assessment, Regulatory

- closer attention to safety margins
- larger animals e.g. dogs, non-human primates
- ICH S7A Guidelines
  - Focused on patient safety- first (acute) studies
  - Required prior to FIH studies
  - Cardiovascular: BP, heart rate, ECG

Development: Risk management and mitigation

- understand mechanism of action

In vivo Cardiovascular Screening Studies: Multiple Approaches Used

Species:

- Rats, dogs, guinea pigs, mini-pigs, nonhuman primates (healthy animals)

Conditions/Protocols:

- Anesthetized vs. conscious, restrained, vs telemetry;
  - Typically single dose studies; BP (SBP, DBP, MAP), HR
    - Mean intervals (data reduction)
  - Anesthesia: allows for greater exposure
    - More instrumentation / measures (dP/dT, CO, SVR, PAP)
    - PK/PD relations with frequent sampling (risk assessment)
  - Conscious studies: environmental conditions critical
  - Statistical power (and positive control) not normally provided
  - Exposures essential for bridging to clinical studies (PK/PD)

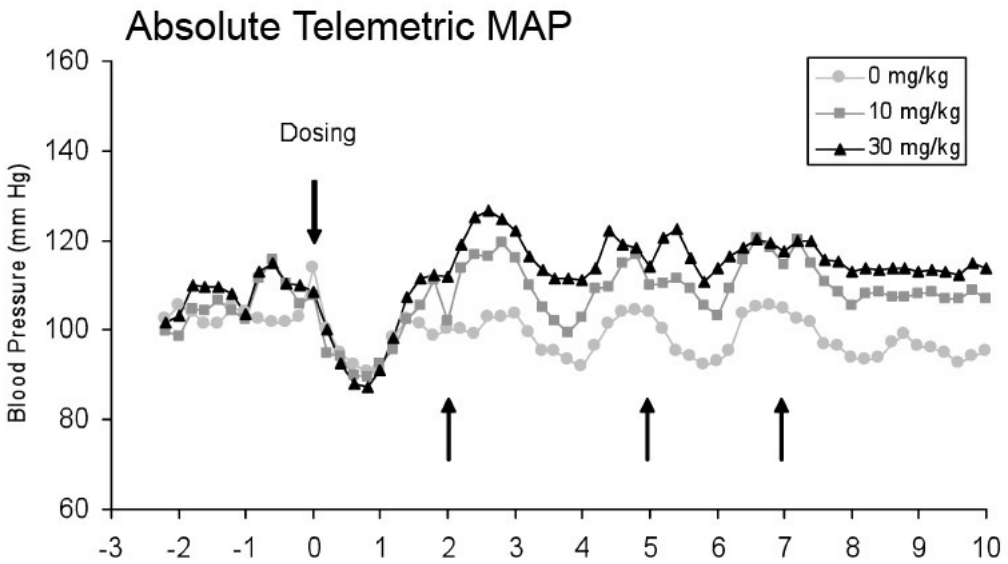
Telemetry Dog Study

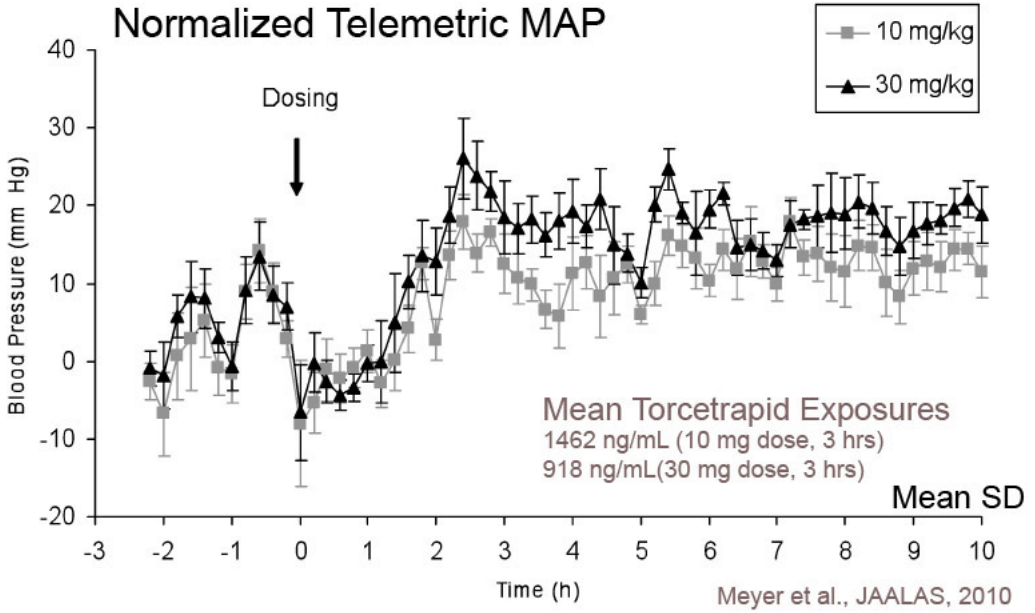
Dose-dependent effects of torcetrapib: 6 dogs, single dose data, 7 day washout periods

-Cage activity (2 5, 7 hours) affects MAP

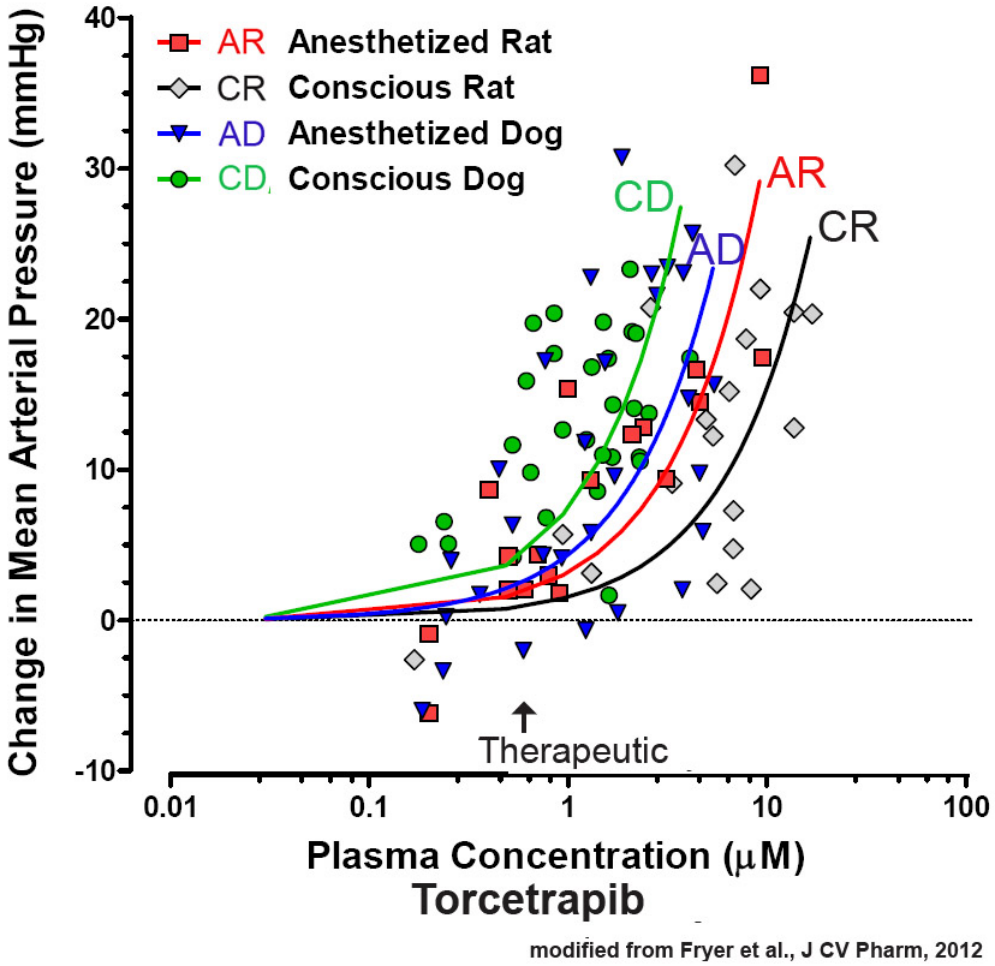
- Emesis: 1 dog 10 mg/kg (at 2 hrs); 3 dogs 30 mg/kg

- Therapeutic human exposures: 210 ng/mL
(Clark et al., 2004)





Cardiovascular Studies with Torcetrapib: 4 Models



modified from Fryer et al., J CV Pharm, 2012

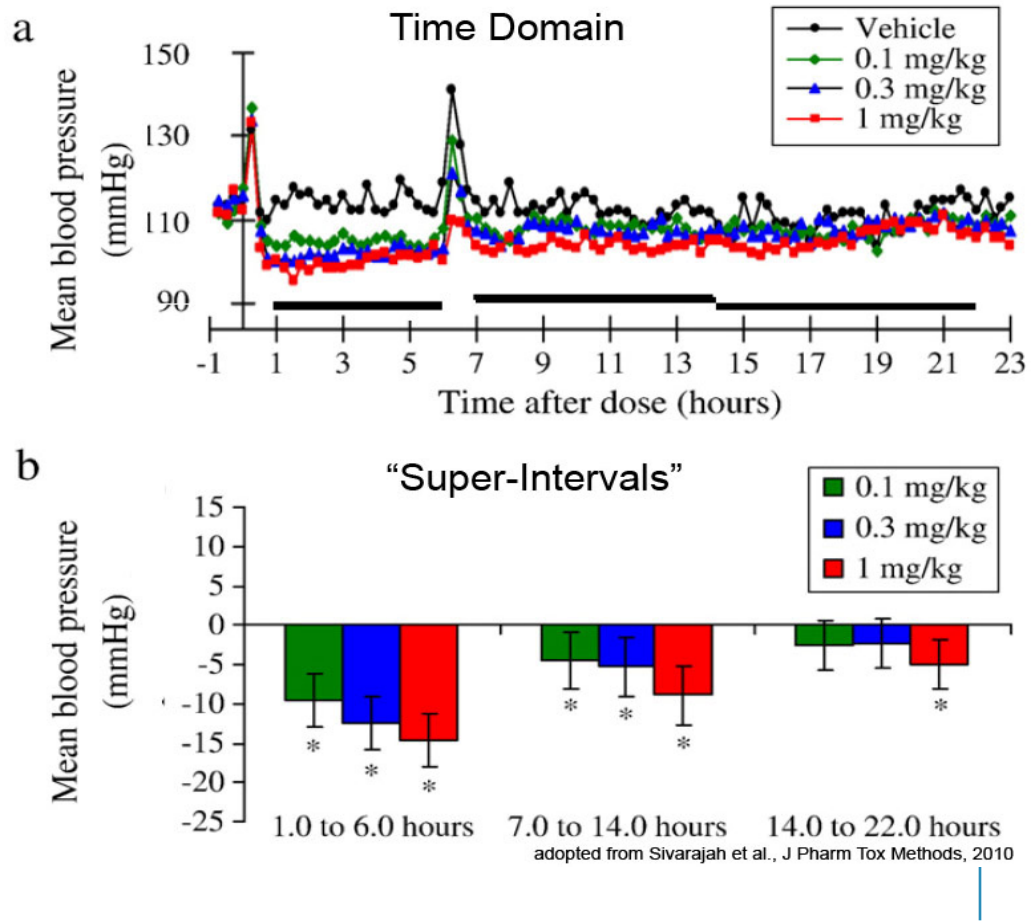
- Variability within/across models

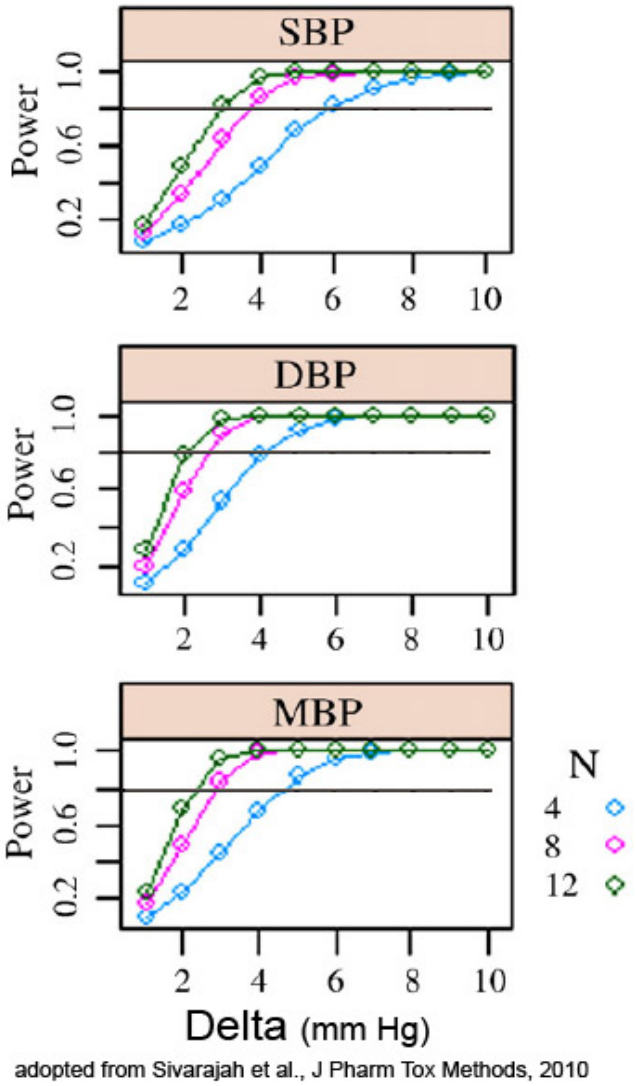
- Translation of effect size to humans uncertain

- One BEST estimate suggests clinical Δ 2-5 mm Hg would be matched in well-designed preclinical study[a]; more data necessary

([a] Leishman et al., J Pharm Tox Methods, 2011)

“Best Case” Preclinical BP Study with Doxazosin: Consistent Canine Telemetry Studies





- Power calculations:18 Pfizer telemetry studies
- Study design, data acquisition, analysis all contribute to power

Preclinical Model Performance: ABPI-Animal Model Framework

Goal: Quantitative method to relate small molecule effects in conscious dog telemetry to Phase I clinical outcome in man involving data sharing across 7 pharmaceutical companies

Data collection:

Qualitative: increase, decrease, no change

Exposure: max exposure with no change **or** min exposure where change occurred

Quantitative: % Δ from vehicle at E_{max}

Exposure: C_{max}

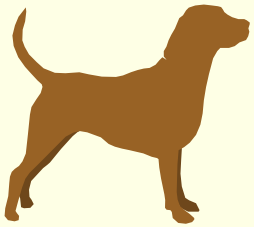
114 small molecules analysed for response in First In Human studies

- 5 compounds increased DBP in man
- 4 compounds decreased DBP in man
- Small number (8%) suggest adequate preclinical screening for phase 1 studies

[1]Valentin et al., 2009 JPTM 60 152-158)

Preclinical Model Performance: ABPI-Animal Model Framework

Limitations in data set

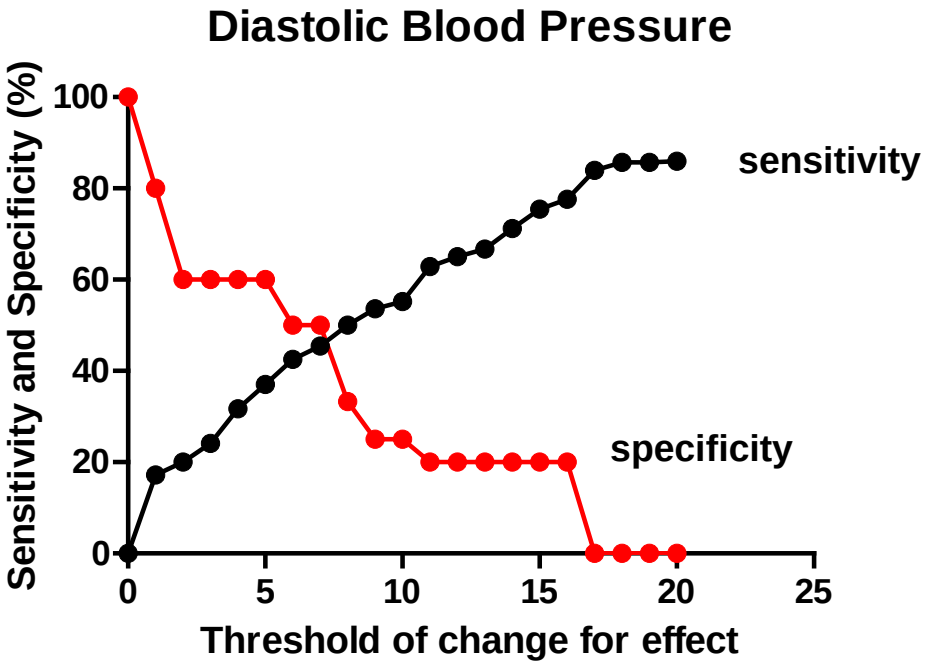


- E_{max} and plasma C_{max} may not occur at the same time point
- Mean data may not provide sufficient data granularity
- Model designs differ across contributing companies
- Statistical power of models vary
- Data bias – Safety Pharmacology filter for Phase I

- Lack of standardisation for Phase I protocols
- Phase I designed to understand safety and tolerability rather than defining specific cardiovascular changes
- Limited guidelines for “normal” ranges for blood pressure and heart rate
- Phase I studies are not statistically powered

[1]Valentin et al., 2009 JPTM 60 152-158)

Preclinical Model Performance: ABPI-Animal Model Framework



- Optimal threshold of change 5% in dog study would provide:
- 37% Sensitivity (probability of dog correctly identifying positive phase I outcome)
- 60% Specificity (probability of dog correctly identifying negative phase I outcome)
- Negative Predictive Value (89%); Positive Predictive Value (10%); Prevalence 1:12

Successes/Gaps & Further Questions

- ICHS7A Guidelines focused on protecting phase 1 volunteers
- High confidence in conscious dog telemetry model predicting compounds without DBP liability in Phase 1
  - Is Phase 1 data adequate “gold standard” for BP assessment?
- “Best Practices” to enhance preclinical/clinical studies
  - Preclinical: Exposures, statistical power calculations, methodologies, data analysis, PK/PD modelling, assay sensitivity
  - Clinical: Methodology, data analysis, PK/PD modelling
- Essential to understand translation to Phase II and beyond
  - Consider inclusion of BP measures in repeat dose studies and/or within “disease” model settings
  - Back translation of clinical case studies; encourage company and regulatory authority interactions to share data