Is More Intensive Evaluation of BP Increases Needed During Drug Development? - Overview

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Think Tank – July 2012

- A CSRC Think Tank was held in July to review many of the issues related to increased BP from drugs being developed for non-cardiovascular indications
- The work from the Think Tank and subsequent CSRC writing group has led to a “White Paper” ready for publication in the *American Heart Journal* in 2013.

Potential consequences of developing drug-induced increases in BP

- Stroke
- Heart failure
- Progression of coronary disease
- Progression of chronic kidney disease
- Loss of BP control in treated hypertensive patients
- Offsets beneficial effects ofconcomitant drug therapy for cardiac, CV, and renal disease
- Unnecessary evaluation for resistant hypertension

Consequences of drug-induced increases in BP may be greater in those with enhanced CV risk

- CV disease
  - NSAIDs, COX-2 inhibitors, acetaminophen increase BP in patients with CV risk and may increase CV events as well
- Chronic kidney disease
  - Greater BP increases seen with certain drugs in chronic hemodialysis patients > CAPD and predialysis CKD patients
  - NSAIDs, COX-2 inhibitors, acetaminophen greater BP increase in CKD patients

Consequences of drug-induced increases in BP may be greater in those with comorbid illnesses

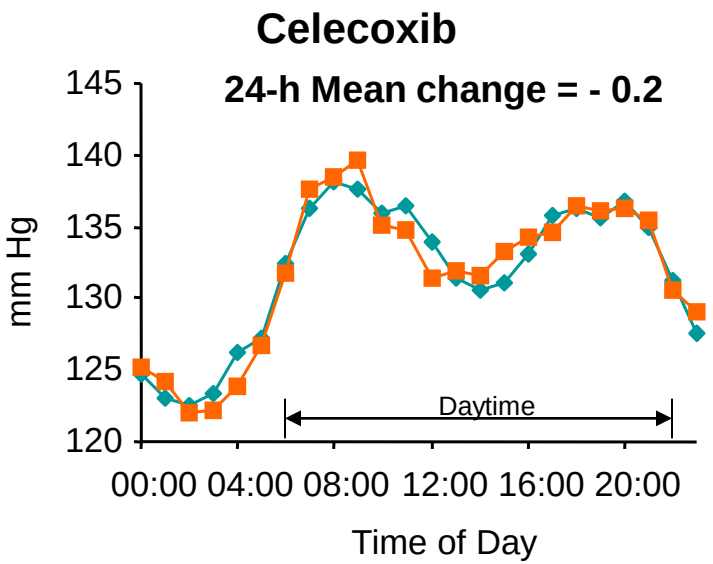
- Diabetes mellitus
  - NSAIDs, COX-2 inhibitors
  - Post-menopausal hormones
- Hypertension
  - VEGF inhibitors induce large BP increases
  - NSAIDS, COX-2 inhibitors
  - Corticosteroids
- Other CV risk factors: Dyslipidemia, smoking, obesity, African American

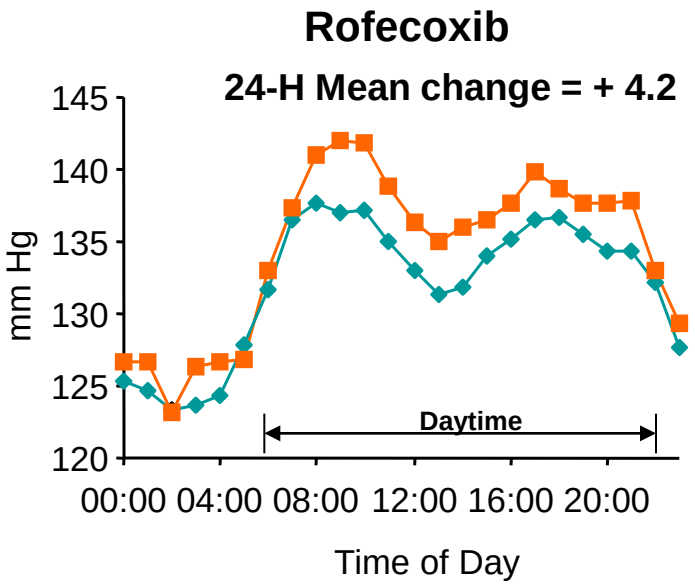
Factors that might influence BP when assessing non-cardiac drugs

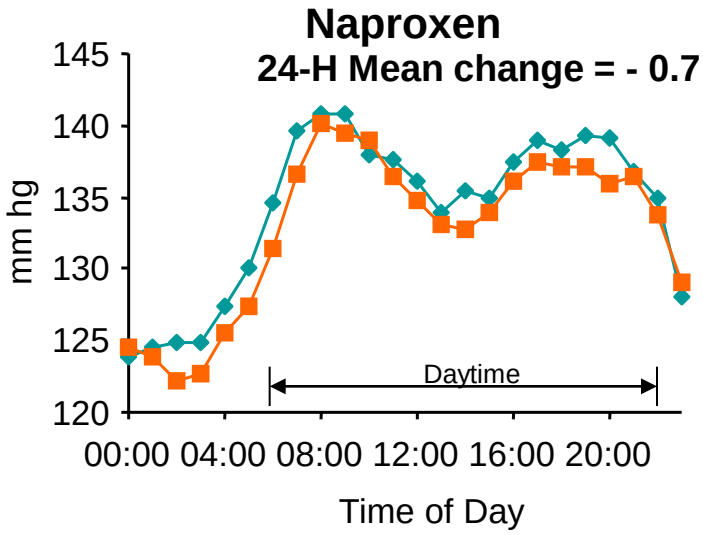
- Method of measurement of BP
- Population studied (e.g., normal subjects *vs* target population *vs* higher risk groups)
- Dose and duration of exposure
- Background therapies that might mitigate BP risk

Central tendency versus outlier values

CRESCENT Trial - 24-hr Systolic BP at Baseline and Week 6 in OA patients with Hypertension and Type 2 Diabetes







Baseline
Week 6

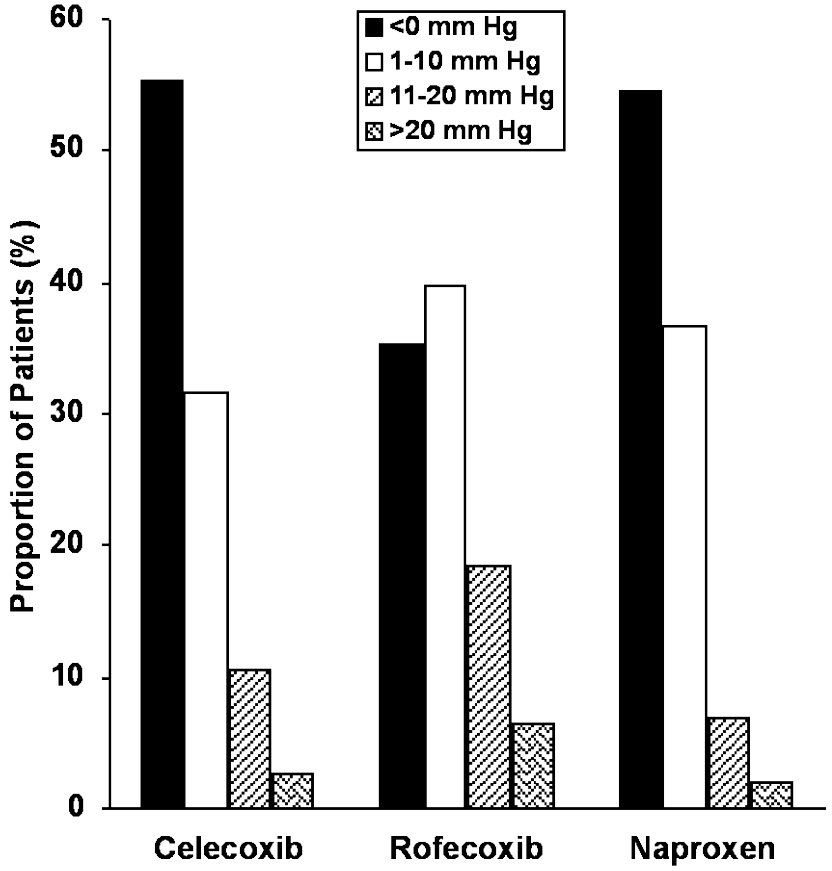
~135/group
Mean age, 62-64 yrs

00:00 = Midnight
ABPM initiated at 09:00 ± 2 hr
Morning dose administered within 5 min of initiating ABPM

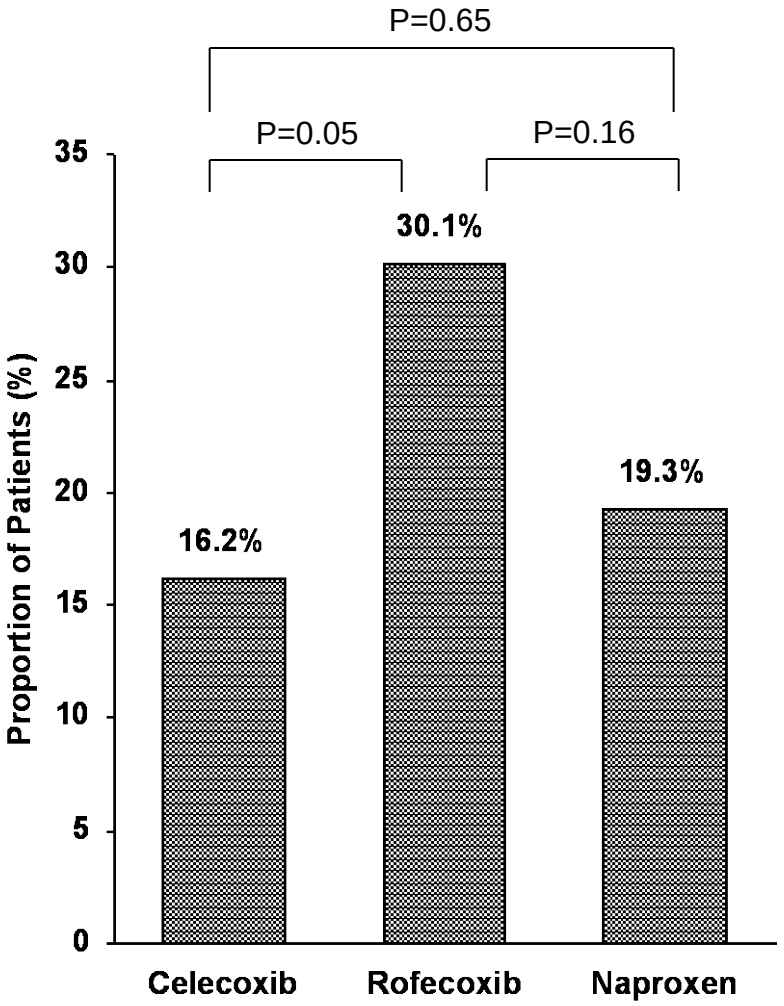
Sowers J and White WB et al. *Arch Intern Med* 2005; 165: 161-168.

CRESCENT Trial – Outlier Analysis in OA Patients with HTN and Diabetes

Distribution of changes in ABPM systolic blood pressure at Week 6



Proportion of normotensive patients who became hypertensive* at Week 6



*Hypertensive: Ambulatory Systolic Blood Pressure ≥ 135 mm Hg

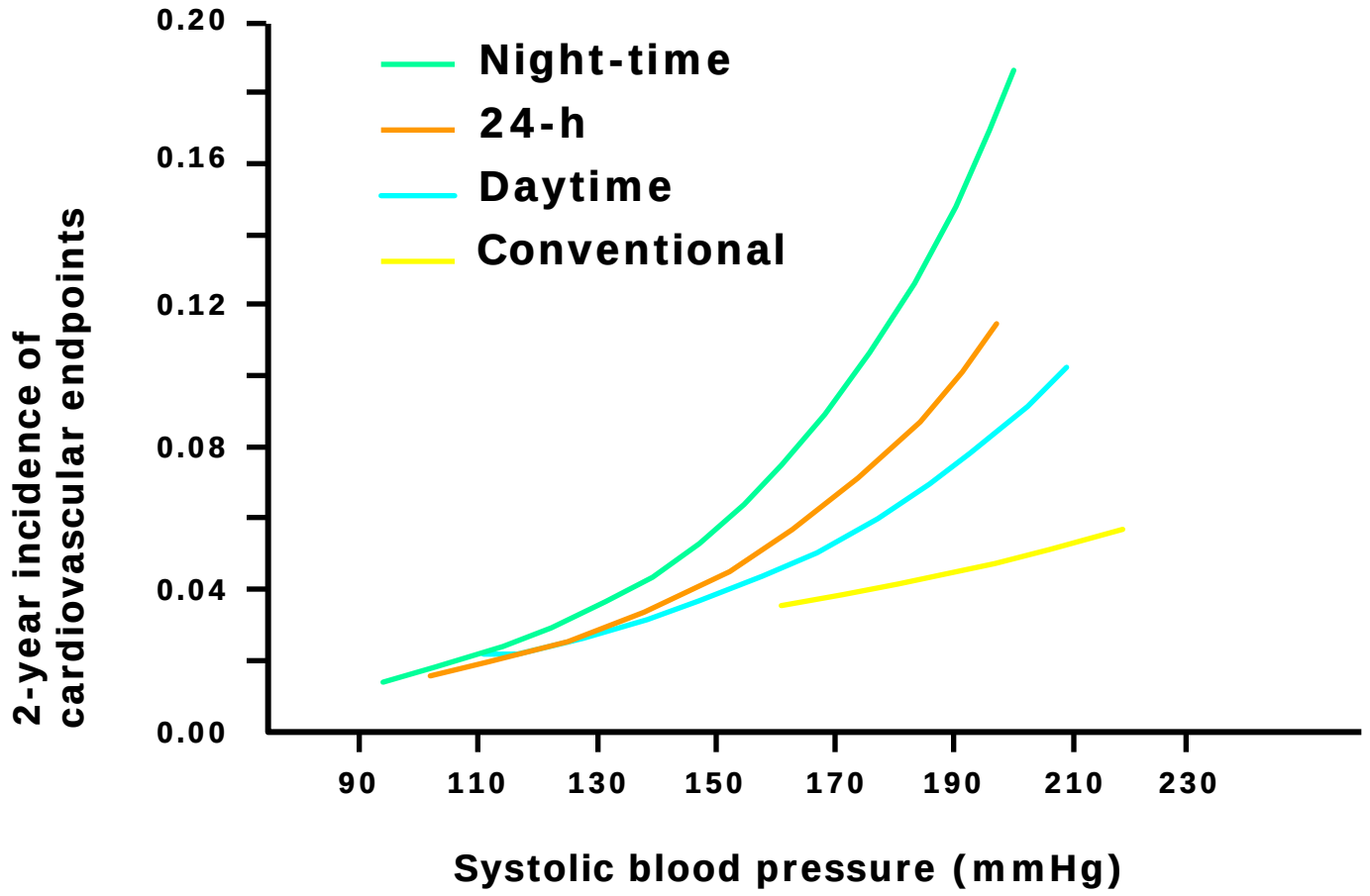
Sowers J and White WB et al. *Arch Intern Med* 2005; 165: 161-8

Do Small Blood Pressure Increases Predict CV Risk in Non-CV Trials?

Do Small Blood Pressure Increases Predict CV Risk in Non-CV Trials?

Not enough data from the literature to answer this question

Conventional, 24-h, Daytime and Night-time SBP as Predictors of Cardiovascular Endpoints (placebo cohort of the Systolic Hypertension in Europe Trial)



Staessen JA et al. JAMA 1999;282:539–46

Mitigation of risks of drug-induced increases in BP may be acceptable or lessened under certain conditions

- Shorter term therapy/lower doses
- BP control of primary hypertension with medication
- Serious disease target for drug in question
- Anticipated regular medical care
- No underlying cardiac, CV or renal disease, or hypertension
- No other risk factors for cardiovascular or renal disease

Drug-Induced BP Increases - Conclusions

Drug-Induced BP Increases: Clinical Implications and Risk Boundaries

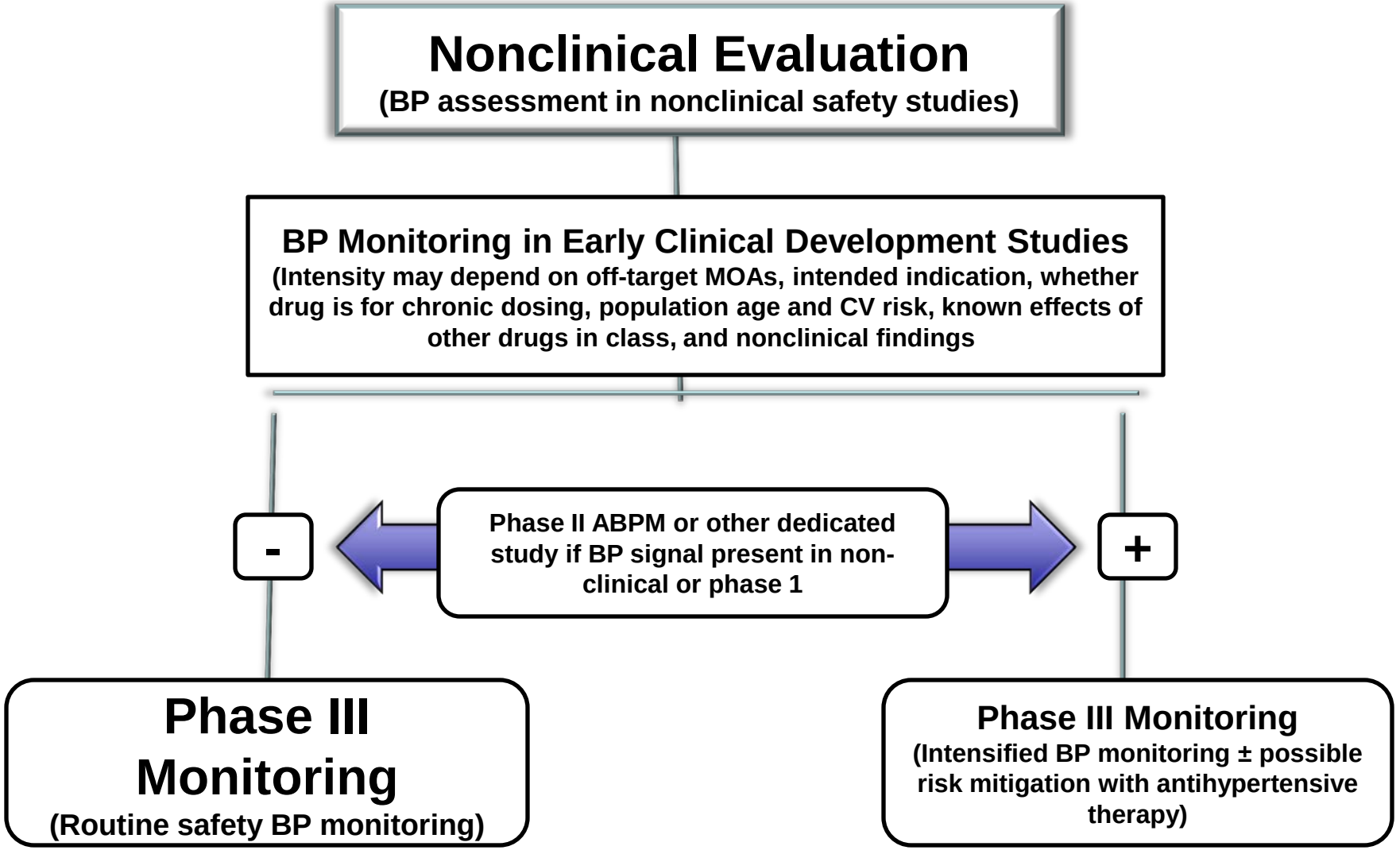
- Approach to BP assessment in drug development will be different from QT/QTc (TQT) approach due to the heterogeneity of mechanisms impacting different patient populations differently
- Changes in systolic BP across all levels are associated with increases in CV risk (particularly stroke and heart failure) with long term therapy
- Methods of BP measurement may impact precision of the signal. ABPM is favored; automated methods can be useful in other settings.
- Changes in BP (drug-induced off-target changes) differences should be evaluated according to baseline BP, age, sex, CV comorbidities, and mechanism
- Observational databases to estimate risk were found to have shortcomings but were overall useful, with the recognition that other methodologies do not exist at this time
- Central tendency increases are usually associated with outlier increases
- There are potential implications of a BP increase being theoretically mitigated by other actions of a drug on underlying risk, but the practical nature of this approach on an individual patient level for small BP increases is questioned
- BP increases may generally be hard to detect and treat by medical practitioners.

Drug-Induced BP Increases: Conclusions

Drug-Induced BP Increases: Technical Aspects of BP Measurement and Need for a Specific BP study

- Devices used for clinical, self- or ambulatory measurement should be independently validated for the population being studied (adults vs children, old vs young, etc). Overall, automated measurements have less variability and better accuracy.
- Precision of BP signals in Phase I studies have not been well studied; standardization of BP monitoring protocols should be enhanced in development programs.
- Dedicated BP studies during Phase II could have value depending on the mechanism of action of the study drug, the population being studied, and the need to understand the need for safety monitoring during Phase III.

BP Assessment Development Processes



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