Assessing BP effects: Mean vs. Outliers

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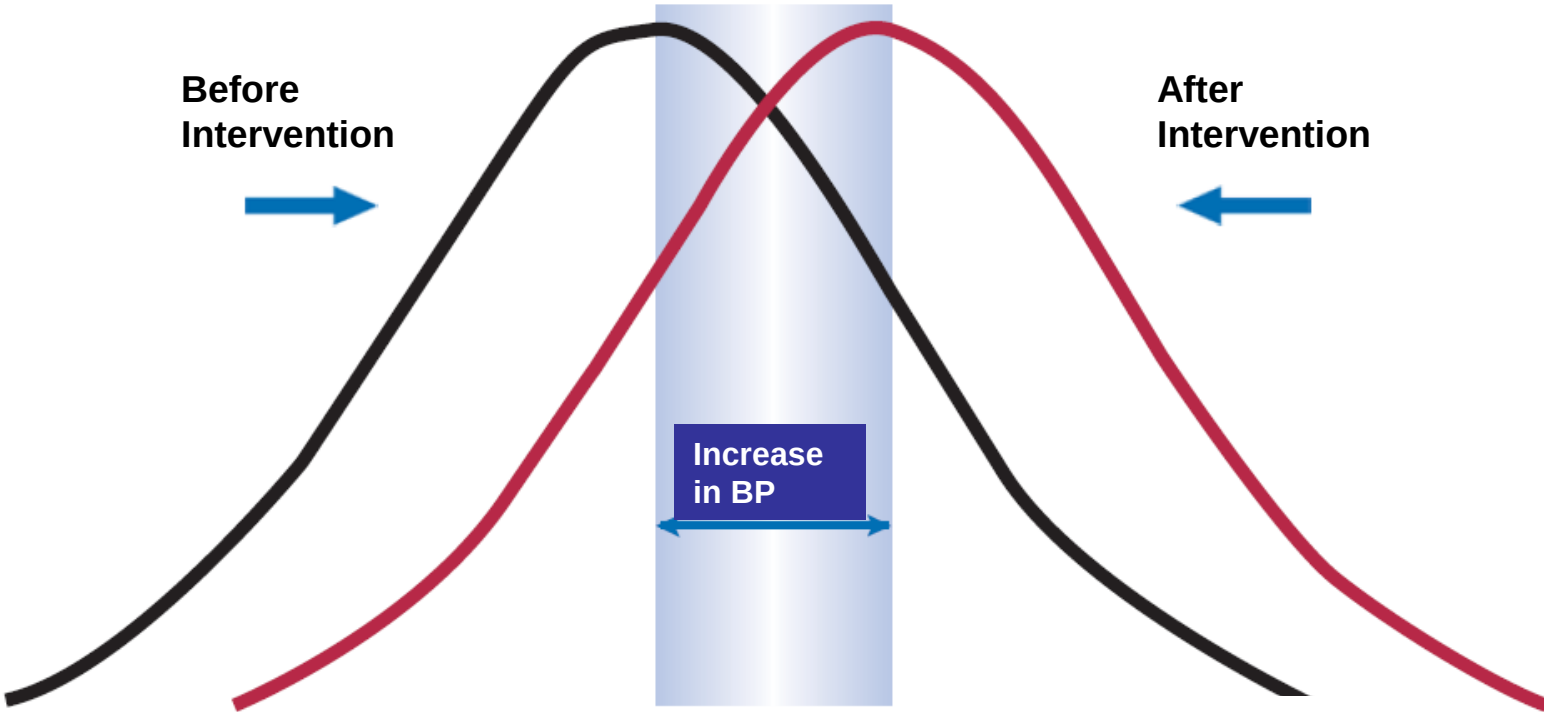
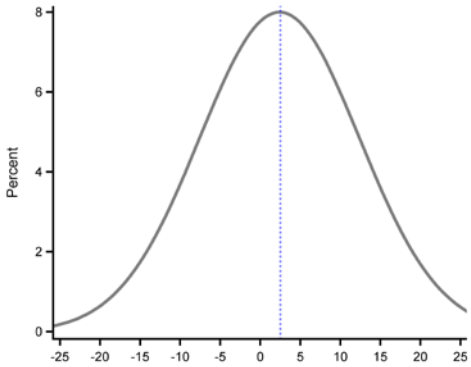
Small increases in blood pressure may have large population effects

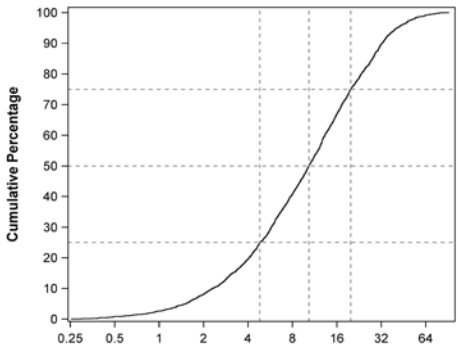


Increase in SBP mmHg	% **Increase** in Mortality		
	Stroke	CHD	Total
2	6	4	3
3	8	5	4
5	14	9	7

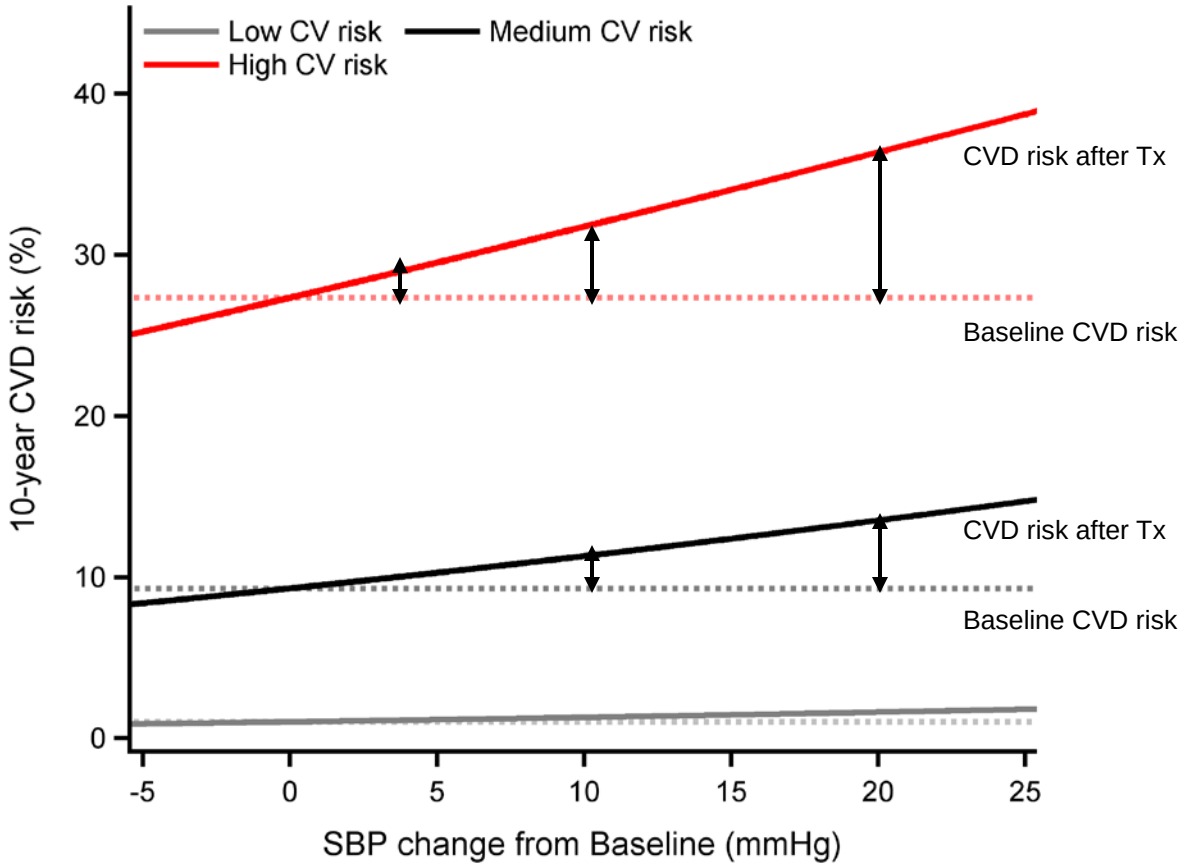
Same BP increase can result in different absolute CVD risk



SBP change from baseline



Baseline 10-year CVD risk (%)



10-year CVD risk is generated based on *General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study – D'Agostino et al. Circulation 2008;117;743-753*

Points to consider

Population risk ≠ Individual risk

- Small BP increases cannot be routinely detected in clinic
- Small/moderate BP increases are unlikely to be significant for patients with low BP/CVD risk
- Some drugs might have differential effects in patient subsets
- Who is at higher risk from increase in BP?
  - SBP increase of > 10 or >20 or >30 mmHg (outliers)
  - Absolute SBP after Tx that results in JNC reclassification
  - Higher baseline CVD risk (e.g. Framingham score)

Potential approaches, if risk only about BP outliers

Identify patients or groups at higher risk

↓

Limit drug use in the population

or

Ensure BP monitoring and treat pharmacologically

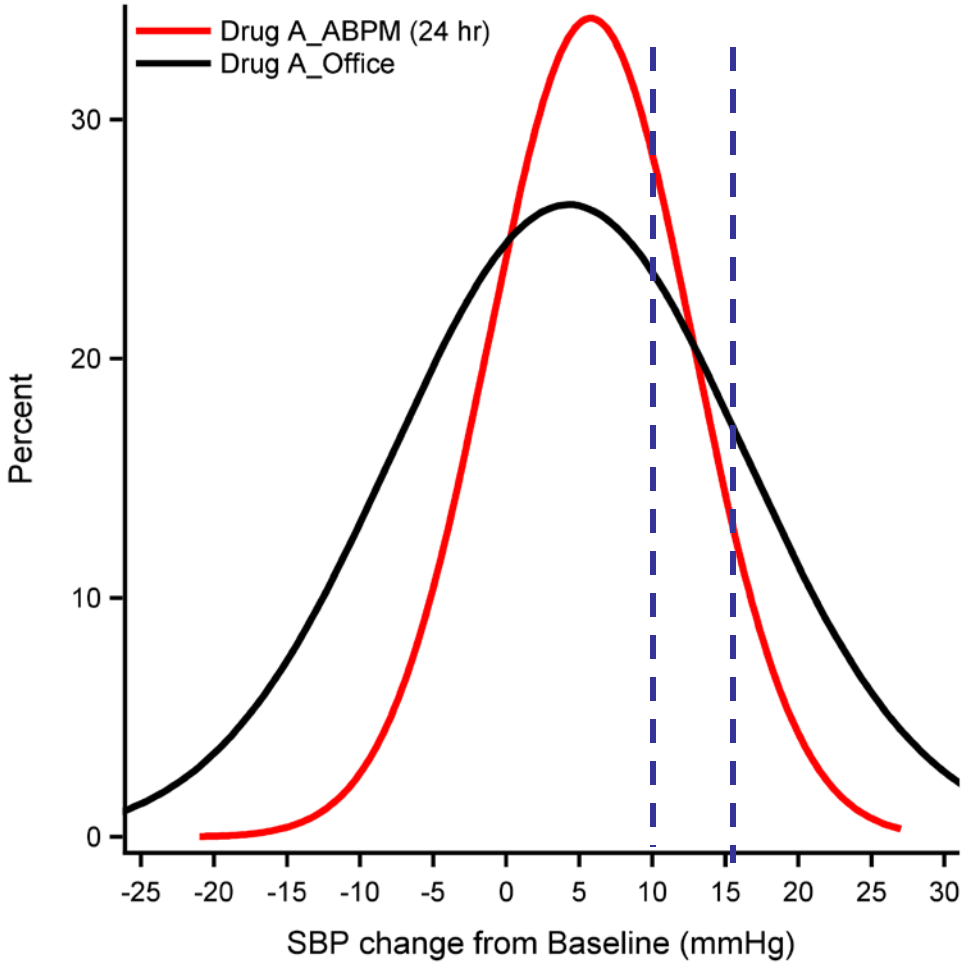
Considering the limitations of office BP measurement, can we really identify individuals & subsets at higher risk?

❖ Impact of the office clinical measurement on assessing BP effects

- Dataset: An ABPM study for Drug A (n ~= 250)
- Patients had both office and ABPM measurements during a 7 week double-blind treatment period
  - 24-hour average ABPM
  - Average of 2 repeated sitting cuff BP measures
- Outcome: change of SBP from baseline at the end of double-blind phase

Large variability in office BP measures

Can we really identify individuals at higher risk?



Mean SBP changes

Drug A

ABPM: 5.8 6.9

Office measure: 4.3 12.1

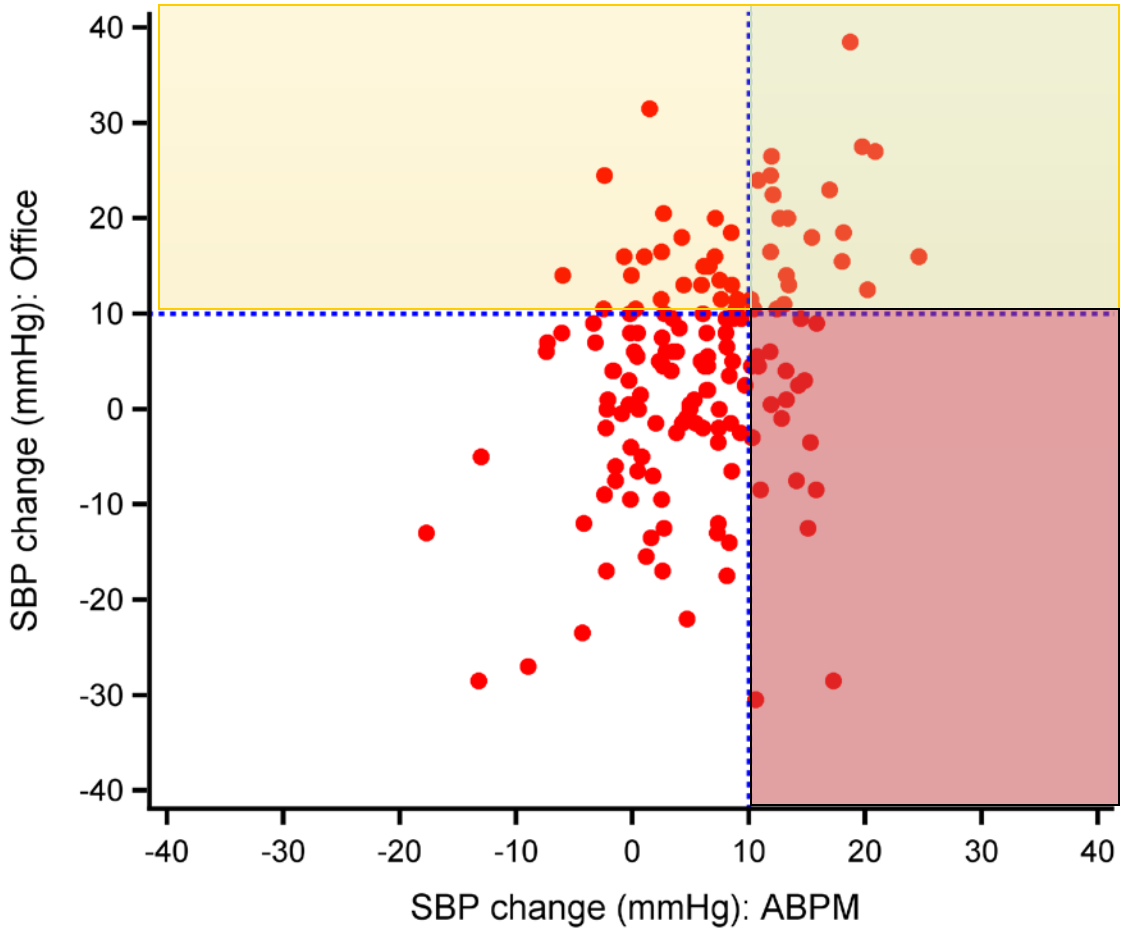
Placebo

ABPM: -0.5 7.5

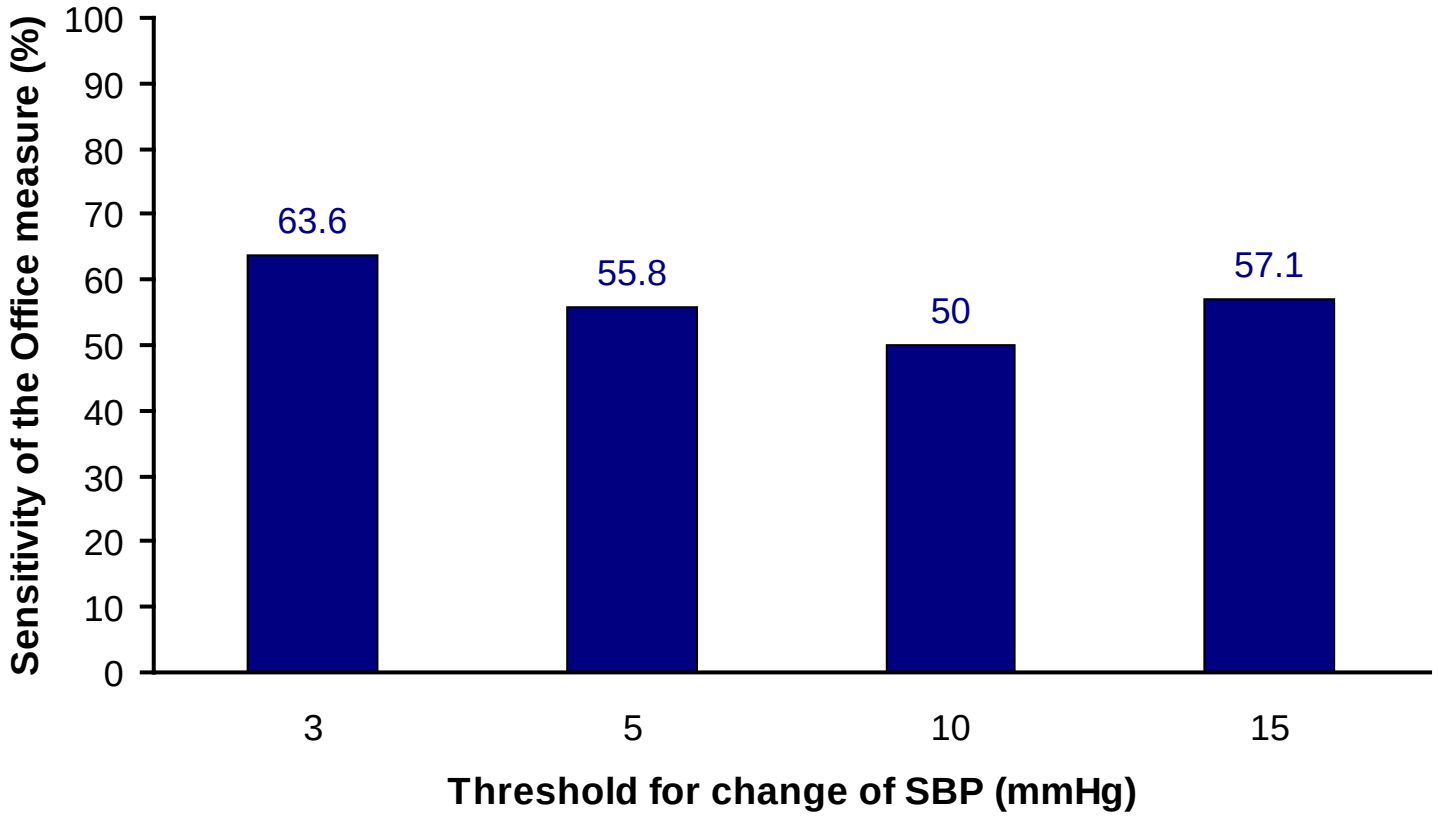
Office measure: -1.9 9.5

Data from a dedicated ABPM study for Drug A

Correlation between two BP measurements for SBP change are moderate (r = 0.34)



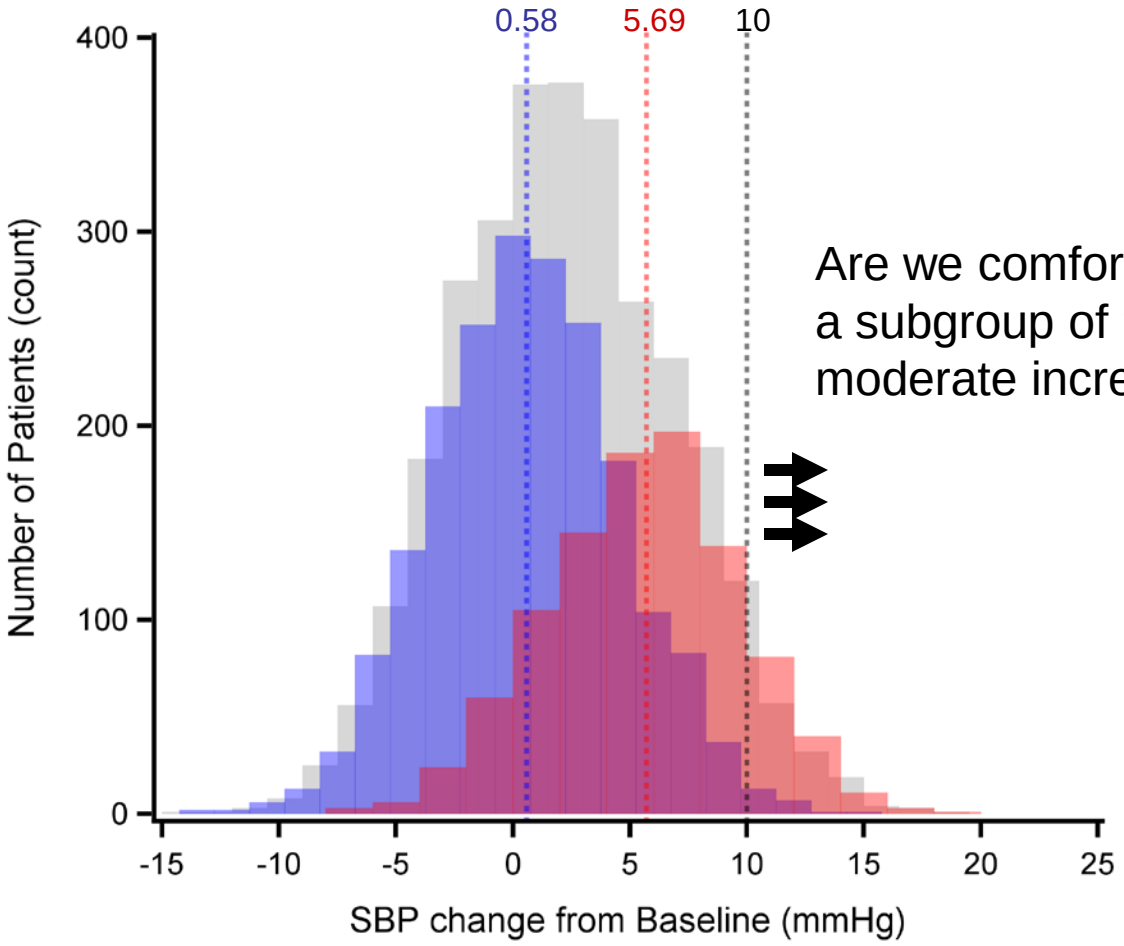
~40-50% of individuals at higher risk* would not be identified based on office BP measures



* Higher risk is defined as a substantial increase in SBP more than a specified threshold

Impact of differential drug effects on BP

targeting outliers might be insufficient



Are we comfortable to leave behind a subgroup of patients with a moderate increase in BP?

Summary

- Drugs that are used chronically and cause small increases in BP (on average) are expected to have large population impacts on increasing CVD risk
  - Individuals with high baseline CVD risk and/or large increase in BP are likely to contribute to a significant increase in absolute CVD risk
- Targeting individuals with substantial increases in BP might be sub-optimal considering:
  - Large variability in office BP measurement presents a challenge in identifying individuals/subsets at higher risk
  - Targeting outliers might not be adequate to detect important subsets at higher risk
- Well-characterization drug effect on BP during drug development is fundamental for any subsequent interpretations and regulatory actions