# Estimates of CVD Mortality Risk Associated with Drug-Induced BP Elevations

Cardiac Safety Research Consortium Thinktank

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# Goal and Outline of Talk

- Use data from an observational study to obtain an estimate of the increased risk of CVD mortality associated with a drug-induced BP increase observed in a clinical trial.
  - Regression dilution bias (def.) and why it is important to consider
  - Magnitude of bias
  - Continuum of CVD risk with BP
- Case example (sibutramine)
- Steps involved
- Other considerations and caveats

# Regression Dilution Bias

- A bias resulting from measurement error and short-term fluctuations within persons that result in under-estimation of the association of risk variables such as blood pressure with disease outcomes

  - The bias DOES NOT impact prediction (e.g., with the Framingham Risk Equation) if reliability of predictors substituted in the equation are similar to those used to estimate regression parameters

  - The bias DOES impact estimates of change in risk based on changes in the risk variable (e.g., estimate of effect of blood pressure change obtained from a clinical trial on change in CVD risk)

# Methods for Correcting for Regression Dilution

- Obtain repeat measurements of the risk factor in a representative sample of the study participants

  - Reliability or intra-class correlation coefficient (ratio of between subject to total variability)

  - Correlation of repeat readings

  - Non-parametric approach

MacMahon S, et al Lancet, 1990
Frost and Thompson SG, J.R. Stat Soc A, 2000

# Logistic Regression Coefficients for Baseline Diastolic BP and CHD Death in 6 Years: MRFT Usual Care Group[+]

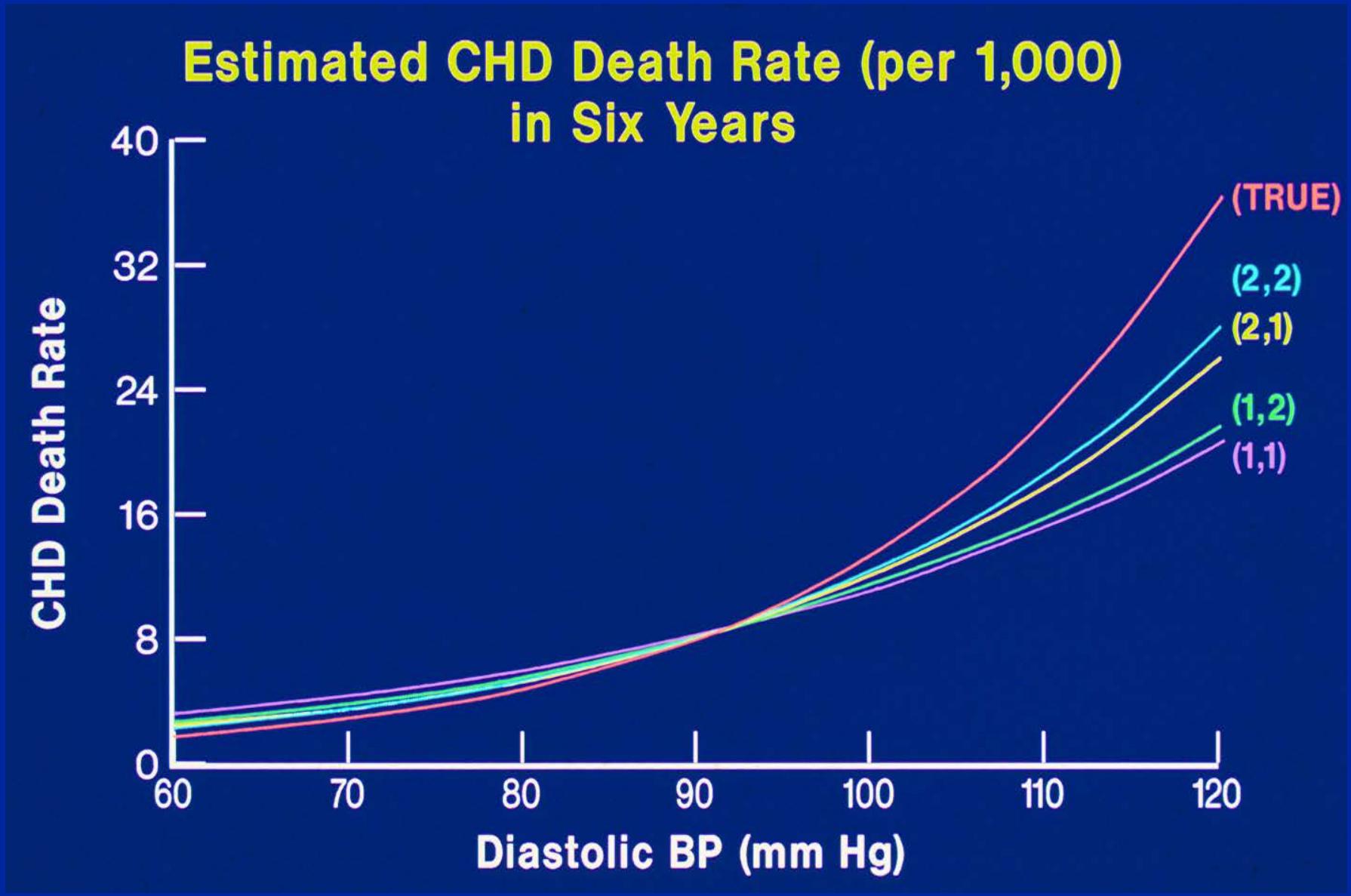
| No Visits | No. Readings | Coefficient ($\hat{\beta}$) | Estimated Risk Reduction (%) per 10 mm Hg Lower[++] |
|---|---|---|---|
| 1 | 1 | 0.0316 | 27% |
| | 2 | 0.0325 | 28% |
| 2 | 1 | 0.0390 | 32% |
| | 2 | 0.0419 | 34% |
| Usual (True DBP) | | 0.0512 | 40% |

[+] Statistics in Med 1992; 11: 1719-1729

[++] $100\,[1 - EXP(-10\hat{\beta})]$

[+++] Reliability coefficient (regression dilution factor) = 0.62

Variance components: Between subject = 58.4 $(mm\ Hg)^2$
Between visits = 26.1 $(mm\ Hg)^2$
Within visit = 10.2 $(mm\ Hg)^2$




Stat Med 1992; 11:1719-1729.

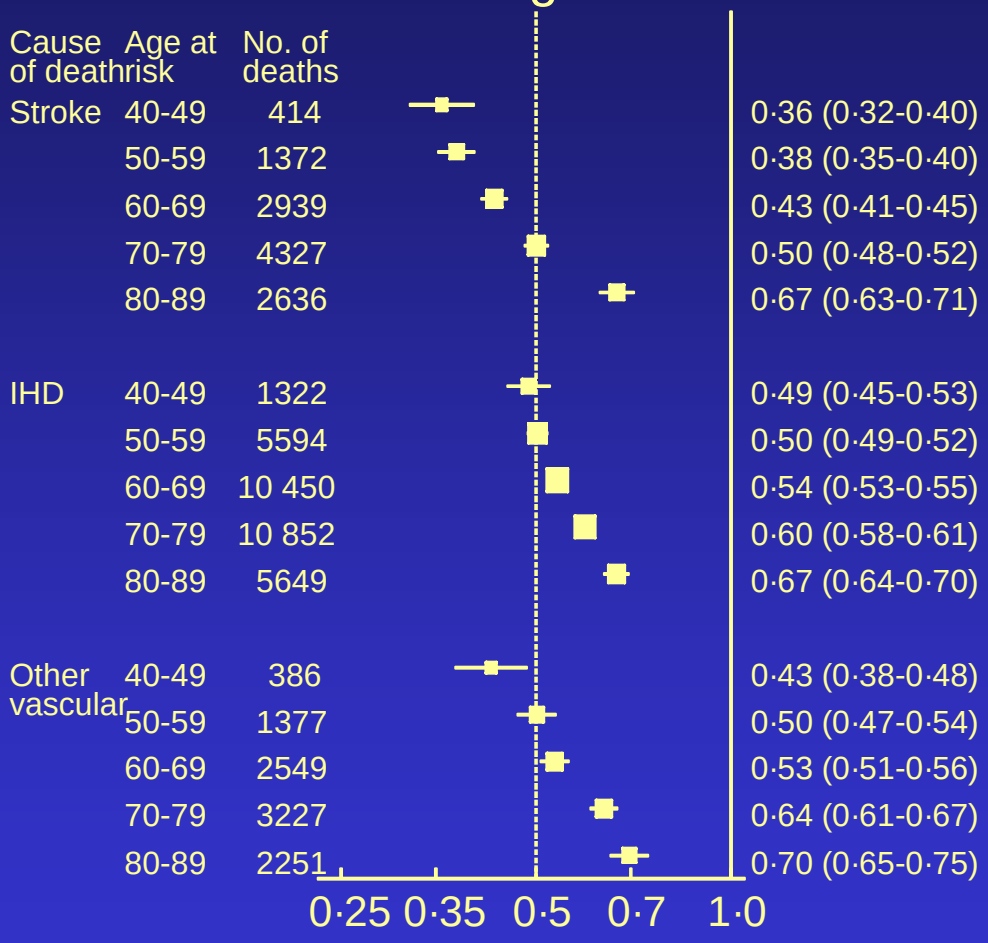
# Usual Blood Pressure and Vascular Mortality

## Prospective Studies Collaboration (Lancet 2002)

- 61 observation studies (N=958,074)
- 56,000 vascular deaths
- Parallel analysis in MRFIT (N=353,168 and 16,784 vascular deaths)
- 162,000 participants with repeat BP after 5 years to correct for regression dilution

# Vascular mortality: Age-specific hazard ratios for 20 mmHg lower usual SBP

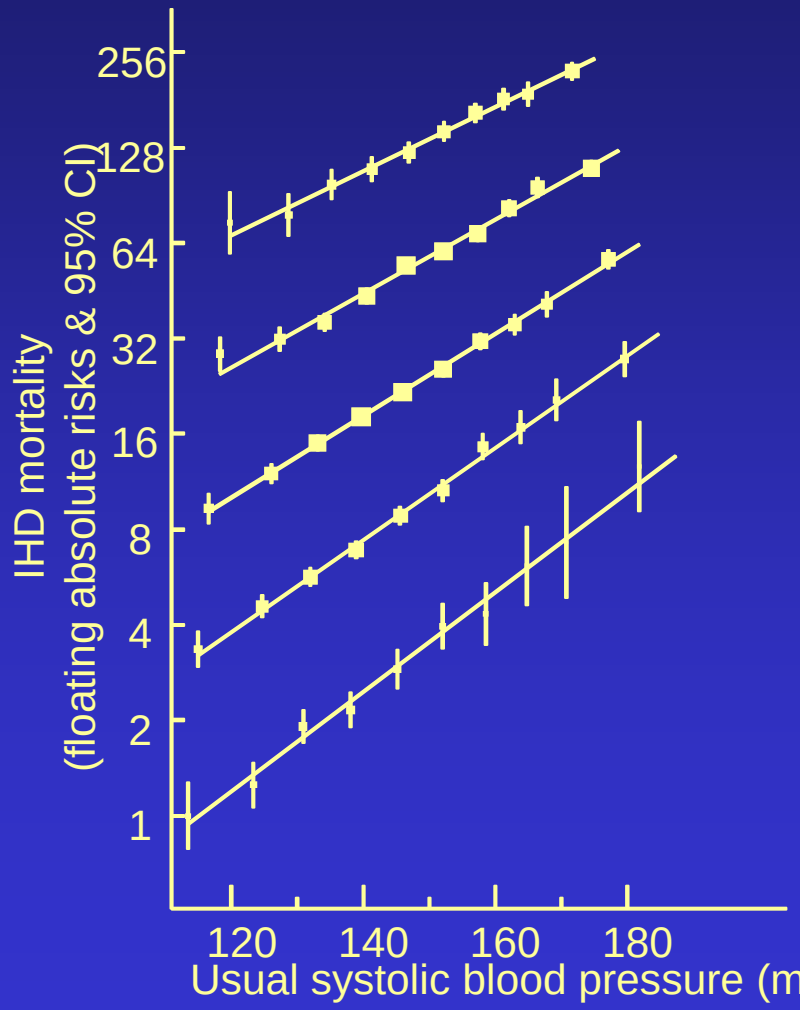
55 345 deaths at ages 40-89




Prospective Studies Group, Lancet 2002.

# IHD mortality rate in each decade of age versus usual SBP at the start of that decade

33 867 deaths at ages 40 - 89

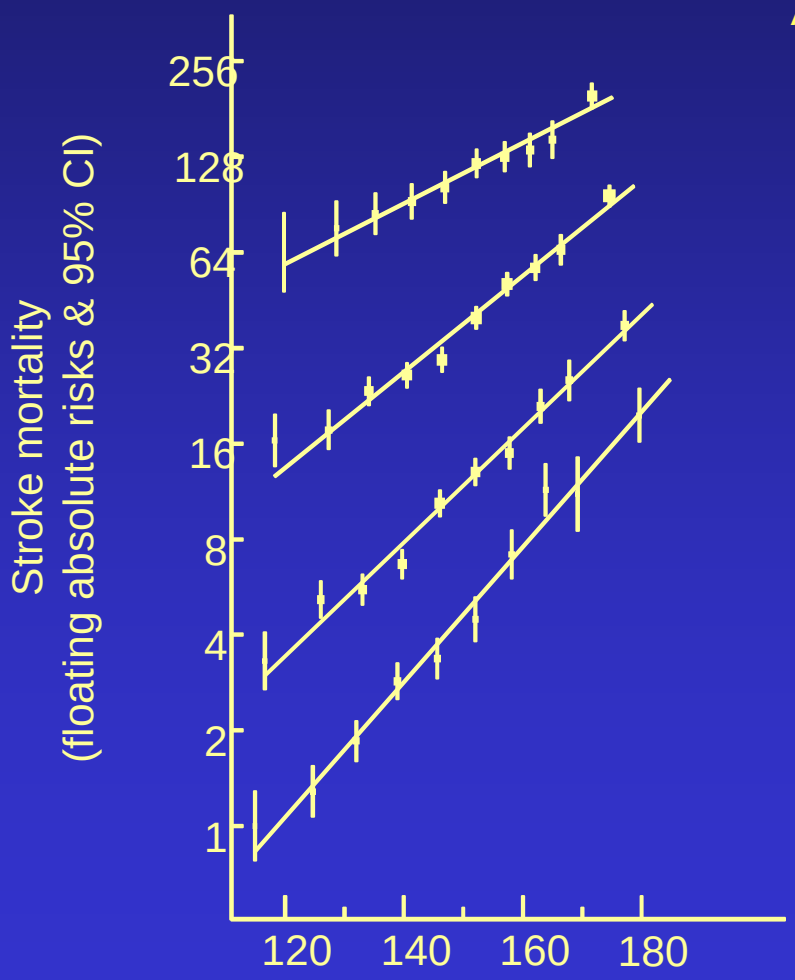



| Age at risk | 20 mmHg ↓ SBP |
|---|---|
| 80-89 | 31% ↓ risk |
| 70-79 | 40% ↓ risk |
| 60-69 | 46% ↓ risk |
| 50-59 | 50% ↓ risk |
| 40-49 | 51% ↓ risk |

Prospective Studies Group, Lancet 2002

# Stroke mortality rate in each decade of age versus usual SBP at the start of that decade

11 274 deaths at ages 50 - 89

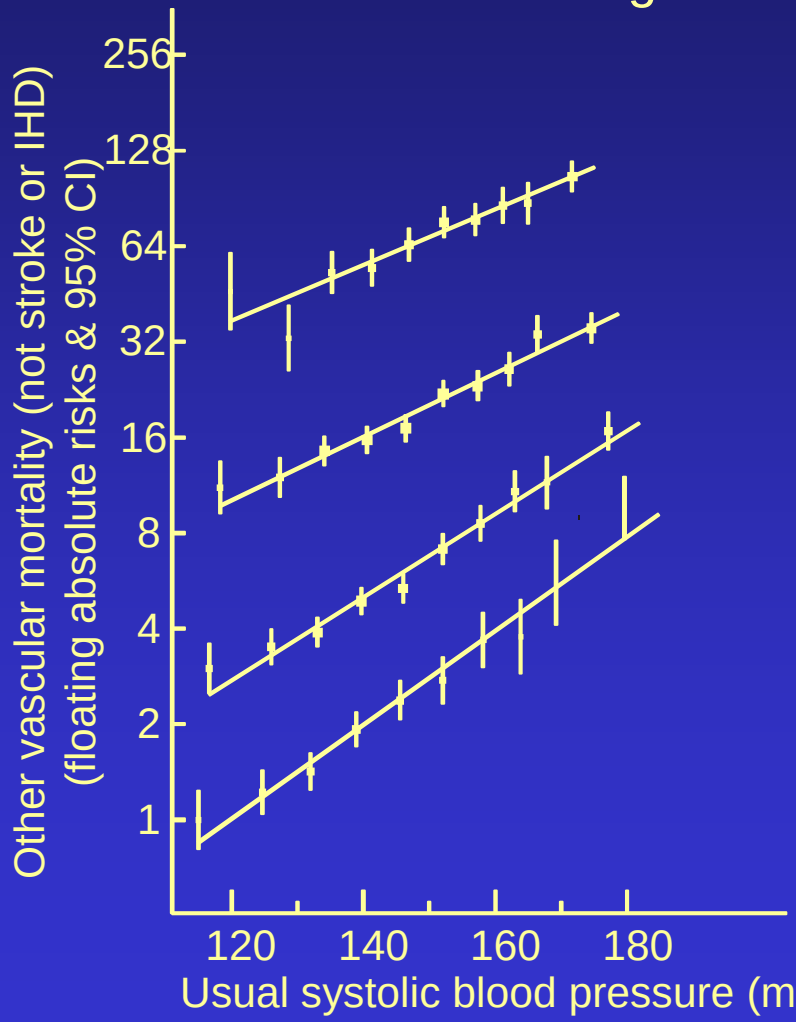



| Age at risk: | 20 mmHg ↓ SBP |
|---|---|
| 80-89 | 33% ↓ risk |
| 70-79 | 50% ↓ risk |
| 60-69 | 57% ↓ risk |
| 50-59 | 62% ↓ risk |
| (40-49 | 64% ↓ risk) |

Prospective Studies Group, Lancet 2002

# Other vascular mortality rate in each decade of age versus usual SBP at the start of that decade

9790 deaths at ages 50-89




| Age at risk: | 20 mmHg ↓ SBP |
|---|---|
| 80-89 | 30% ↓ risk |
| 70-79 | 36% ↓ risk |
| 60-69 | 47% ↓ risk |
| 50-59 | 50% ↓ risk |
| (40-49 | 57% ↓ risk) |

Prospective Studies Group, Lancet 2002

# Estimated Increase in Risk of Vascular Mortality Associated with Systolic BP Increases

| Systolic Blood Pressure Increase (mm Hg) | Estimated Increase in Mortality[+] | | |
|---|---|---|---|
| | CHD | Stroke | Other CVD |
| 1.0 | +3.0% | +4.1% | +3.1% |
| 1.2 | +3.6% | +4.9% | +3.7% |
| 2.0 | +6.0% | +8.1% | +6.1% |
| 3.0 | +8.8% | +11.9% | +9.1% |

[+] Based on risk estimates in Prospective Studies Collaboration, Lancet 2002, men and women aged 60-69.

SCOUT trial (sibutramine) estimate

# Summary of Steps for Estimating Increased Risk Associated with Drug-Induced BP Increase

1. Obtain estimate of effect of treatment on BP from randomized trial (i.e., relative to placebo)
2. Estimate BP → risk relationship from observational studies that can reliably estimate risk (e.g., Prospective Studies Collaboration)
3. Using repeat measurements of BP for sample in observational studies to estimate regression dilution factor
4. Adjust BP → risk relation for regression dilution
5. Use “adjusted” slope to estimate potential risk increase

# Other Considerations and Caveats

- Magnitude of excess risk depends on underlying risk of population for which the drug is indicated.
- May not be relevant to treatment used for short duration
- Risk likely depends on underlying reason for BP increase
- Standard errors for “adjusted” regression coefficients are increased as well as regression coefficients (not an issue in studies like MRFIT or Prospective Studies Collaboration)