

# Lessons learned from E14

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# E14?

- It is an ICH Guidance
  - ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  - E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

# Noisy link of QT to arrhythmia

ECG

↓ \*

QT (biomarker) =  $f_1(\text{HR}, [\text{drug}])$

↓ \*

QTc =  $f_2([\text{drug}])$

↓ \*

Arrhythmia =  $f_3(\text{QTc})$

+

{Other mechanisms of arrhythmia (false -)}

-

{Stabilizing drug effects (false +)}

# Result of uncertainties

- E14 asserts a MID for QTc
- QT effects are dichotomized on this MID
- “Regulatory certainty” at the expense of
  - A nuanced appreciation of risk
  - Discouraging development of some benign or acceptably toxic drugs

# Is BP a better surrogate?

- We behave as if it were...
  - Established basis for approval of drugs
  - Guidance and labeling reflecting expected benefits
  - No threshold for treatment

# Support of BP as surrogate

- Epidemiology

# Effects of BP on CV Outcomes

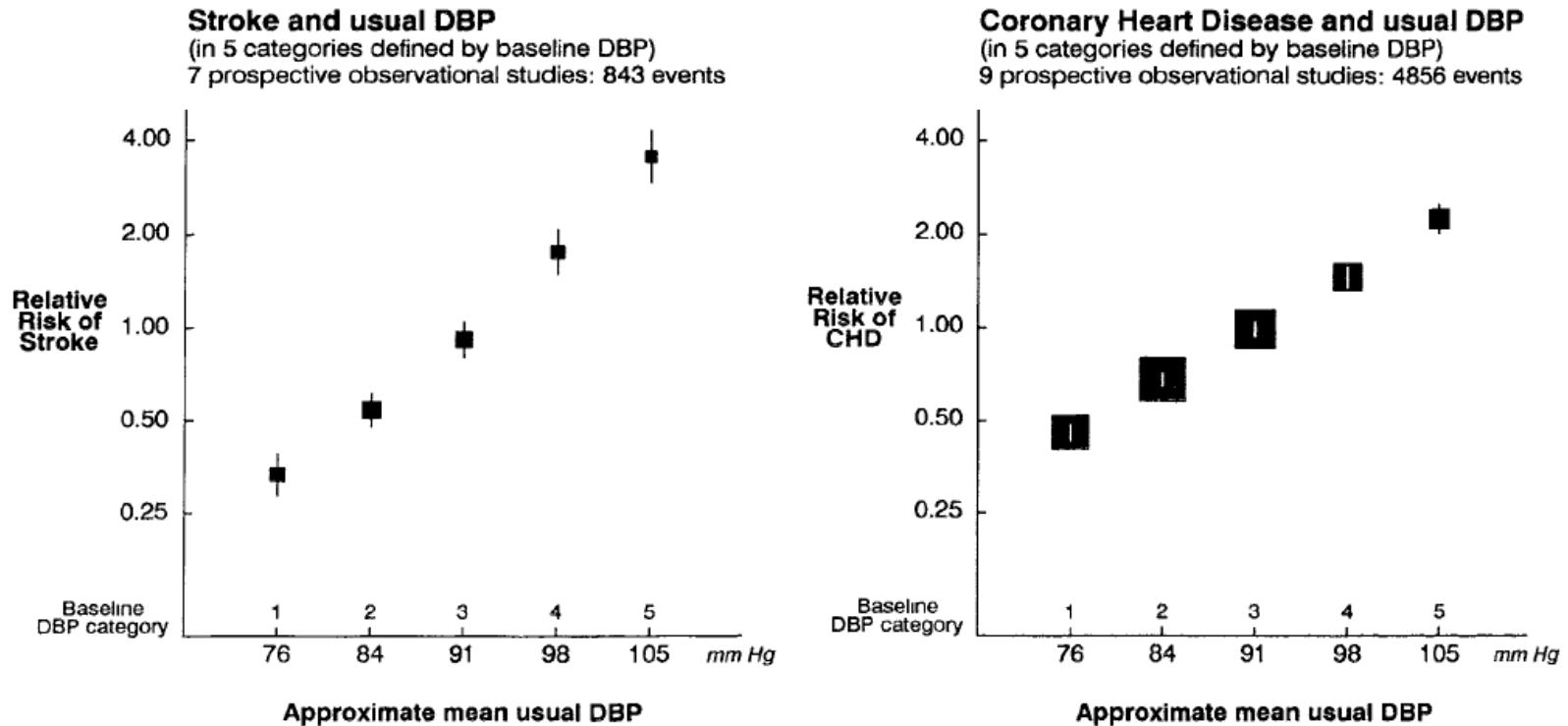
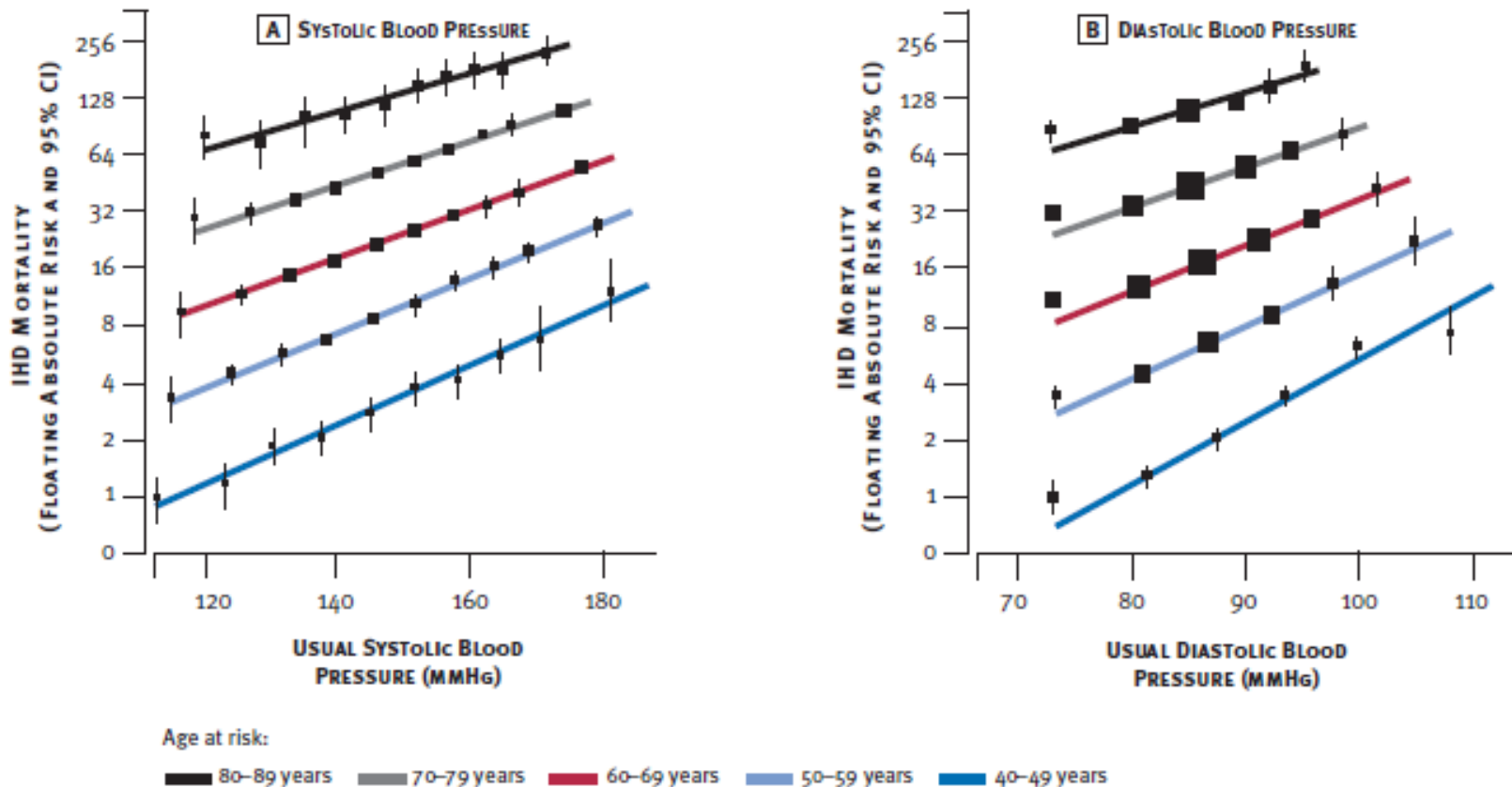


Fig 1—Relative risks of stroke and of coronary heart disease, estimated from combined results.

- MacMahon et al., 1990 Lancet 335:765-774.
- Similar relationship holds for effects of antihypertensive drugs

# Other Risk Factors—Age

**Figure 9.** Ischemic heart disease mortality rate in each decade of age versus usual blood pressure at the start of that decade





# Support of BP as surrogate

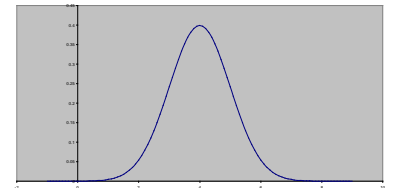
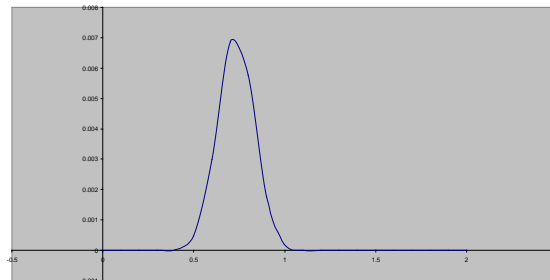
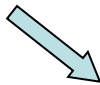
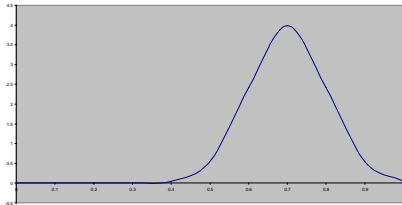
- Epidemiology
- Outcome studies
  - with a wide variety of drugs from many drug classes, bearing in common
    - not site of action
    - not mechanism of action
    - only reduction in BP
  - achieve risk reduction largely equivalent to having an untreated BP at new level

# High Quality Data with BP

- Better data on harm associated with BP enables an approach that is more quantitative and less arbitrary

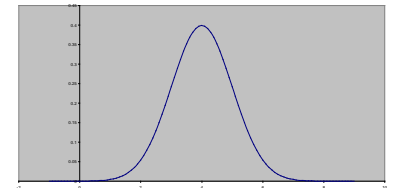
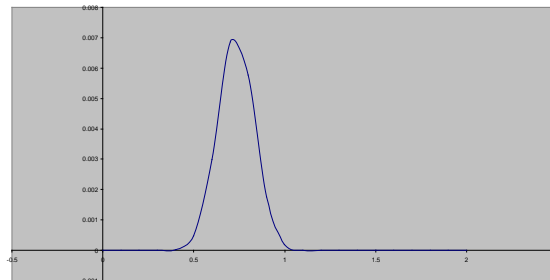
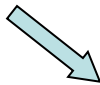
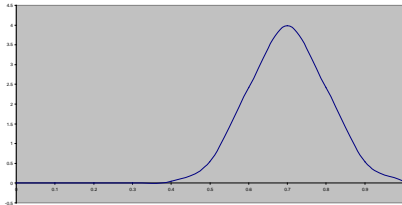
# Assessing Benefit (Symptoms)

- Value of benefit
  - High for death, stroke
  - Low for wrinkles
  - Mean, distribution
- Effect size is absolute change in symptom
  - Comes from studies
  - Mean, distribution
  - CI is f(nature, power)



# Assessing Benefit (Events)

- Value of benefit
  - High for death, stroke
  - Low for wrinkles
  - Mean, distribution
- Effect size is absolute change in likelihood of event
  - Comes from studies
  - Mean, distribution
  - CI is  $f(\text{nature, power})$

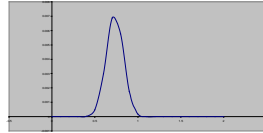


# Assessing harms

- Similar process, if you have the data
- Similar dependence of CI on power
- See Dr. Madabushi's worked example
- Need to get on same scale as benefits (QALY or similar)

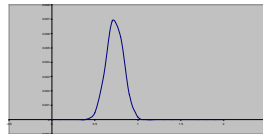
# Assessing multiple benefits or harms

- Death



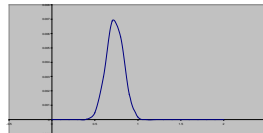
- MI

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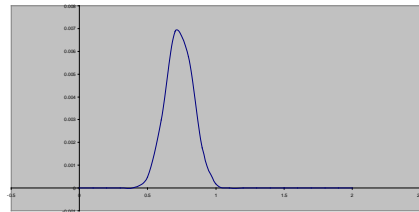


- Stroke

+

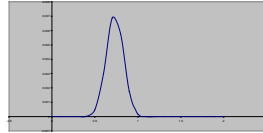


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- Net

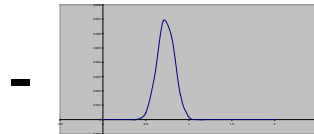


# Assessing net benefit or harm

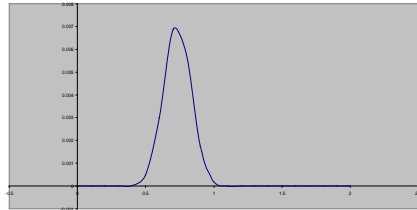
- Benefit



- Harm



- 
- Net



# How BP is not like QT

- Because you know something quantitative about the risks, you can...
  - Apply what you know quantitatively about benefits
  - Make rational, defensible R-B decisions
  - Adjust the population to ensure net benefit