Estimation of the proportion of patients who benefit from a treatment in a positive randomised trial, using a novel Variance-Guided equation

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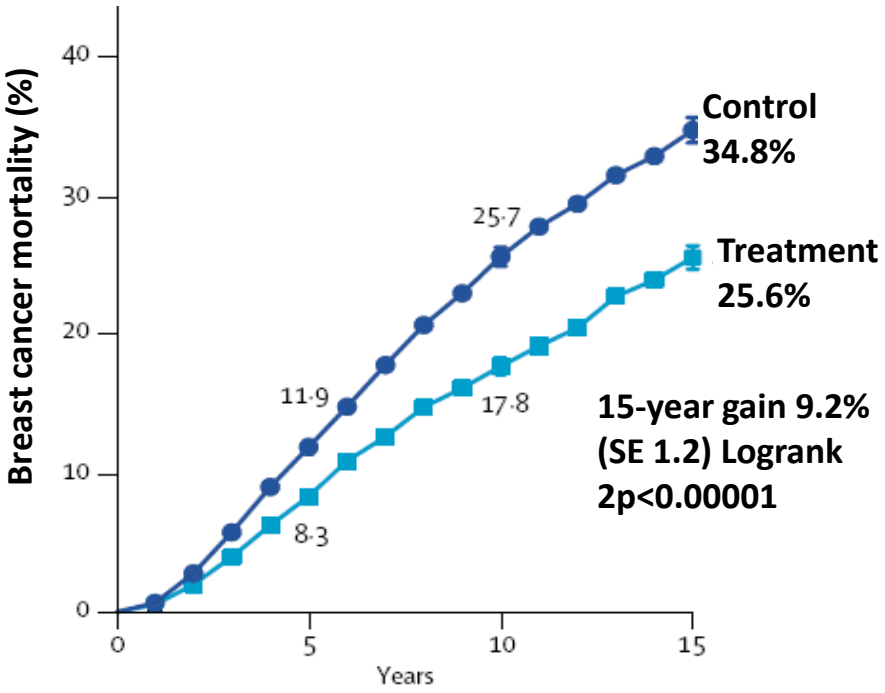
The Problem

From the results of a positive randomised clinical trial, it cannot be ascertained whether the additional benefit is distributed to all patients or is limited to only a subgroup.



For example, from these data one can derive that there is a 9.2% reduction in mortality.

Does this mean…

- **Every patient's life span is increased by 9.2%?**

Or

- **Only 9.2% patients benefit and the other 90.8% derive no benefit?**

Or, most plausibly,

- **Only a proportion of patient's life span is increased (by >9.2%) and the other patients derive no benefit? *If so, can this proportion be estimated?***

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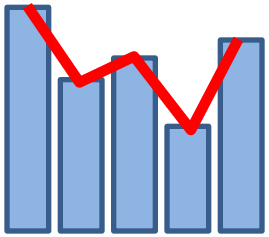
A New Insight
– A new Variance-Guided equation

The variance in length of survival in the treated group will be same as the control group if the treatment is effective in every patient; but will be different if the treatment is effective in only a subgroup.

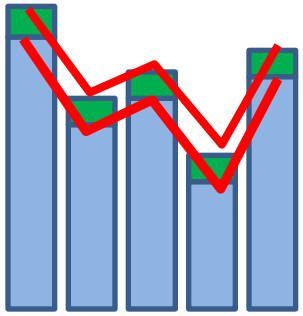
Column height = Survival of an individual patient

Waviness of the line = Variance

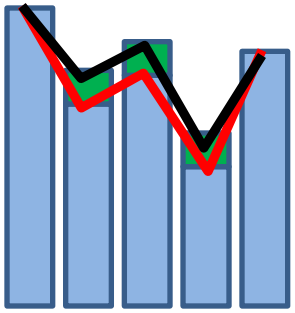


$$P = \frac{1}{1 + \frac{S_1^2 - S_0^2}{(\mu_1 - \mu_0)^2}}$$

If everyone benefits, the variance remains constant



If only some benefit, the variance changes by an amount related to the proportion who benefit



where,

μ_0 = mean of log (*survival*) for the control

μ_1 = mean of log (*survival*) for the treated

S_0^2 = variance of log (*survival*) for the control

S_1^2 = variance of log (*survival*) for the treated

variance = (number of events) x (standard error)^2

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Testing the equation with real-world data

The Scottish adjuvant tamoxifen trial (n=1323)

Adjuvant tamoxifen vs. Not

1978 – NOT selected for ER status

Conveniently, ER status determined in 742

Using the raw survival data from the trial, we calculated the variances and survival times in each arm

Using these values in the new equation, we estimated the value of ***P*** and compared it with the actual % ER positive.

Results - Does it work?

Our prediction:

Without using any information about the ER status, our equation independently calculated that ***P*** = **64% derived some benefit.**

36% derived no benefit.

The reality:

In 58.6% ER > 19 fmol/mg protein

In 70.6% ER > 4 fmol/mg protein

59% to 71% derived some benefit

29% to 41% derived no benefit.

Therefore, our prediction is consistent with reality

Could be further tested on other trials (HERA, ATAC, etc.)

Impact

- **Widely applicable to clinical trials of chemo-, hormone, radiation or biologic therapy**
- **Estimate the exact proportion who benefitted and who did not benefit**
  - ***A more precise consultation***
  - ***Get new biological and therapeutic insights into mechanisms of disease.***

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