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From FBM (Faith-Based Medicine) to EBM (Evidence-Based Medicine): easy to say

As we say today, "in God we Trust; we Need Data from the Rest". Even knowing that the absence of evidence is not evidence of absence. And what better evidence in clinical research than the outcome of randomized clinical trials? Well-designed and well-executed, since it is immoral to conduct bad clinical trials.

We all accept that a clinical trial:

1. Should ask an important question,
2. Should answer it reliably,
3. Should produce clinically important outcome, and
4. Should be widely practicable.

And all the above, because, in the daily medical practice, our patient is expecting a positive answer in his following questions:

1. Is it good for me?
2. How it is good and for how long?
3. Is it better than the current? And finally,
4. Am I included in the population supposed it is applicable?

Remember the last. It is crucial.

In a randomized controlled trial (RCT), subjects are randomly assigned to an experimental or a control intervention. Beneficial or harmful effects of the experimental intervention are usually evaluated by comparing the number of events in the experimental and control groups, using measures such as the relative risk (RR) or the relative risk reduction (RRR). However, there is a main disadvantage of using relative measures of treatment effects in clinical decision-making, as they do not reflect the magnitude of the risk without therapy (baseline or underlying risk). For example, when the baseline risk is extremely low, even an effective treatment has no scope to show efficacy.

Thus, to take into account the baseline risk, the absolute risk reduction (ARR) is often presented as an additional measure of clinical effectiveness. However, the ARR may be difficult to incorporate into clinical practice. In contrast, another parameter, the number needed to treat (NNT) provides a way of expressing the effect of a treatment in clinical terms. Nevertheless, the NNT should always be interpreted in its clinical context. Information should be given about the experimental intervention (drug, dose, duration, etc) and about the control intervention against which the experimental intervention was tested (placebo, no treatment, etc). By examining the magnitudes of NNT (and NNH, number needed to harm), the clinician can start to make risk-benefit decisions tailored to the individual patient's needs [1].

Recently, I was reading an interesting article on the evaluation of cancer drugs and the common practice to set as end-point in the clinical trials for cancer drugs the progression-free survival versus the overall survival [2]. And my mind went back to our patient's questions. So, I turned to my colleague Stefanos to prepare for me an example on the issue of starting making risk-benefit decisions tailored to the individual patient's needs.

Stefanos came back with the following example:

The trial: The Breast Cancer Prevention Trial [3] was a randomized, placebo-controlled, 6-year study of the effects of tamoxifen (20 mg once daily for up to 5 years) in a population of women (n = 13,388) at elevated risk of breast cancer. To be eligible for the trial, women had to be 60 years old or to have a projected 5-year risk of invasive breast cancer equal to or greater than that of an average 60-year-old woman (1.66%). The Breast Cancer Prevention Trial found that tamoxifen treatment produced a 49% reduction in the risk of invasive breast cancer in the population of women at elevated risk. There was no statistically significant evidence of heterogeneity of relative risks of invasive breast cancer across groups defined by age, number of affected first-degree relatives, or projected 5-year risk of invasive breast cancer. We therefore assume that the relative risk reductions from tamoxifen for invasive breast cancer are uniform across all subgroups.

Let us go now to the application of effect measures in the Breast Cancer Prevention Trial.

1st clinical question: What was the reduction in risk of invasive breast cancer within one year, among women at elevated risk of breast cancer who were treated with tamoxifen (20 mg, once daily) in the Breast Cancer Prevention Trial? [3]

Average annual event rate of placebo group: 0.676%

Average annual event rate of tamoxifen group: 0.343%
Relative risk = 0.51
Relative risk reduction = 0.49
Absolute risk reduction = 0.333%
Number needed to treat (for 1 year, with tamoxifen 20 mg, once daily) = ***300***

2nd clinical question: What was the increase in risk of deep vein thrombosis within one year, among women at elevated risk of breast cancer who were treated with tamoxifen (20 mg, once daily) in the Breast Cancer Prevention Trial? [3]
Average annual event rate of placebo group: 0.084%
Average annual event rate of tamoxifen group: 0.134%
Relative risk = 1.60
Relative risk increase = 0.60
Absolute risk increase = 0.050%
Number needed to harm (for 1 year, with tamoxifen 20 mg, once daily) = ***2,000***

The conclusions (and the decision) yours!

Mine? The decision is quite easy: NNT surpass NNH. Is it though so obvious always what to recommend? You probably agree with me that from a clinical trial to clinical implementation quite (?) often you come face to face with the so called clinical gap. And then you start thinking what they say about statistics: never having to say that you are sure.

But others have said it better: Statistical analysis is not enough. For a difference to be different it must make a difference. In other words, the importance hides under the clinical influence of the individual.

And as William Osler declared once, "If it was not of differences among individuals, the Art of Medicine could be science in addition".

Definitions [4]

Event rate is the number of people experiencing an event as a proportion of the total number of people in the population,

Relative risk (RR) is the ratio of the event rates of the two groups. It may be calculated as: (Event rate in the treatment group) / (Event rate in the control group),

Relative risk reduction (RRR) is the difference in event rates between the two groups, expressed as a proportion of the event rate in the control group. It is usually constant across populations with different risks. It may be calculated as: 1 - RR,

Absolute risk reduction (ARR), also called risk difference, is the arithmetic difference between two event rates. It varies with the underlying risk of an event in the individual patient. It may be calculated as: (Event rate in the treatment group) - (Event rate in the control group),

Number needed to treat (NNT) is the number of patients who would have to receive the treatment for 1 of them to benefit. It may be calculated as: 100 divided by the absolute risk reduction expressed as a percentage (or 1 divided by the absolute risk reduction expressed as a proportion).

Number needed to harm (NNH) is the number of patients who would have to receive the treatment for 1 of them to experience an adverse effect. It may be calculated as 100 divided by the absolute risk increase expressed as a percentage (or 1 divided by the absolute risk increase expressed as a proportion).

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