Do Clinical Trials Tell us All the Truth? Relative Versus Absolute Risks and their Influence on the Therapeutic Decisions of Cardiologists

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Brotons et al[1] demonstrate in this number of the journal how different ways of presenting the results of clinical trials can affect perception of the effectiveness of different treatments and influence the decision to prescribe drugs in different cardiovascular prevention scenarios. The authors analyzed the attitudes and perceptions of Spanish cardiologists toward the primary and secondary prevention of ischemic heart disease by means of a survey that was made of the members of the Spanish Society of Cardiology. An advantage of this study is that it used three types of questionnaires that were assigned randomly to participants. In addition, each questionnaire presented several clinical scenarios and asked questions about the physicians´ attitudes and preference for different preventive treatments in different clinical scenarios. Nevertheless, one limitation of the study is that it did not allow for changes in the perception and therapeutic attitudes of each physician in relation to the type of information presented for evaluation. Each physician received only one type of questionnaire (with information presented in one way). On the other hand, there was a notable imbalance between the number of cardiologists who received questionnaires in the relative risk format and those who received it in the absolute risk or number of patients needed to treat (NNT) formats. In addition, the rate of participation was only 40%, which is another important limitation to generalizing the results of this study.

On the other hand, the conclusions reached coincide with those obtained in similar studies that have been published.[2-5] This is additional consistent evidence of the existence of a tendency to overestimate therapeutic

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effectiveness when the classic estimators of effectiveness (relative risk) are used instead of indicators of therapeutic effectiveness (absolute risk).

One of the objectives of evidence-based medicine is to improve therapeutic decision-making through a critical evaluation of the most relevant medical bibliography by interpretation of the results and their application to daily practice. Most clinical trials published present their results as relative risk (proportional benefit), the interpretation of which is clinically complex and subject to confusion. Taken alone, relative risk is not very useful for decision-making. For example, a reduction of 10% in a rare episode could be considered a trivial benefit, whereas the same reduction in a common episode has great impact on public health. In reality, relative risk is useful mainly in research, but not for reaching decisions about a specific patient because it does not estimate the impact of the benefit on the population, as estimators of absolute risk do. That is to say that to make a correct therapeutic decision it is not enough to know that the intervention has a beneficial effect, it is also necessary to know the magnitude of this effect.

For example, to expect that the treatment of mild hypertension will produce the same benefit in an individual as is obtained in relative terms (a 40% reduction in the risk of infarction in a large meta-analysis of experimental studies[6]) can be ultimately frustrating. When the effectiveness of treatment is measured in absolute terms, that is to say, when the part of the risk that is unmodified by the intervention is subtracted from the observed benefit (in our example, the cardiovascular episodes that occur with treatment), the theoretical benefit of 40% for treatment decreased to 2%. The idea that the baseline risk of patients influences the absolute benefits that can be expected from an intervention has been widely discussed in the cardiovascular bibliography. Rose[7] called attention years ago to the fact that the baseline risk of individuals participating in primary prevention trials was less than that of patients recruited in secondary prevention trials. This explains to a great

TABLE 1. **Benefits of treating five cardiovascular problems. Number of patients needed to treat (NNT)**

Problem	Episode	Years of follow-up	Baseline risk	RRR	NNT
DBP 115-129 mm Hg	Death, stroke, AMI	1.5	0.13	89	3
Coronary bypass	Death	5	0.32	56	6
Aspirin for TIA	Death, stroke	2.2	0.23	31	6
Hypercholesterolemia	Death, AMI	7.4	0.12	14	89
DBP 90-109 mm Hg	Death, stroke, AMI	5.5	0.05	14	141

Adapted from Laupacis A, et al. N Engl J Med 1988;318:1728-33.

extent why the benefit of the intervention is usually smaller in primary prevention trials than in secondary prevention trials. This means that the small benefit that can be expected from intervention is easily surpassed by any small adverse effect associated with the intervention («small risks can eclipse small benefits»). In fact, this principle must be considered before making any recommendations about prevention on a large scale.

Various authors have demonstrated the advantages of presenting the results of studies of therapeutic effectiveness as the absolute reduction of risk (ARR or NNT) instead of the relative reduction of risk (RRR), since RRR does not take the baseline level of risk of the subjects into consideration, as was commented above. This can be easily verified by comparing the same treatment in two situations with different levels of risk: moderate and mild arterial hypertension (AHT). ARR simply expresses the benefit specifically attributable to the therapeutic intervention. It is calculated by subtracting the risk observed in the active treatment group (Pa) from the risk observed in the control group (Pc), which is usually higher (ARR=Pc–Pa). On the other hand, as its name indicates, NNT is an index derived from the previous concept, which estimates how many patients must undergo the intervention proposed to avoid an episode. Mathematically, NNT is the reciprocal of ARR (NNT=1/ARR). In our example, the NNT indicates that the clinical effort to avoid one case of infarction is exactly one-half for the treatment of moderate AHT as for mild AHT. Laupacis et al[8] have calculated the individual benefits (NNT) of treating various cardiovascular conditions, comparing different factors and cardiovascular diseases (Table 1).

An additional advantage of the NNT index is the possibility of applying it in an individualized way to any patient with any level of risk, whether greater or smaller than that of the patients included in the clinical trial of reference. For example, imagine that we have calculated that a patient has approximately one-half of the risk of the patients in the reference trial using a risk equation. One possibility would be to adjust the NNT obtained in the trial mentioned by a factor of «f» (the difference in risk between our patient and the patients in the trial), and to calculate an NNT adjusted for the patient´s risk (NNT-a). In our case 13/0.5=26 patients. This adjustment can also be made for factors like, for example, follow-up time, which allows therapeutic regimens of different duration to be compared.

The NNT can also be used to calculate the risk-benefit ratio of a treatment or as guidance to choose between several therapeutic alternatives. For example, consider any situation in which there are two treatment options, both of which produce the same results but are of different utility for the patient. A clinically more reasonable index is «NNT adjusted for differences in expected utility.» This index indicates that, to avoid an episode, on the average, it would be necessary to treat X more patients with the option that is less useful for the patient than with the option that is more useful.

An area of research of special interest at present is the treatment of medical information by clinicians and its influence on decision making. Recent studies, such as the one mentioned above, demonstrate consistently that the degree of enthusiasm of physicians with certain preventive treatments, such as AHT, depends fundamentally on how the results of the most relevant trials published are presented.

Naylor et al[2] and Forrow et al[3] have observed, in family practitioners and internists, that most (close to 90% in both studies) are very willing to use antihypertensive drugs when data are presented as RRR. Nevertheless, when the data were presented as ARR, only 46% of the physicians surveyed were in favor of incorporating the treatment supported by the trial into their daily practice.

Similar studies made with patients have demonstrated that the patients, like the physicians, were more inclined to accept the proposed treatment when the information on its potential benefit was presented as RRR. In a recent study, Hux et al[9] demonstrated that 89% of the patients diagnosed *de novo* as mild AHT accepted the treatment when its benefits were presented as RRR, versus 45% when benefits were presented as ARR. However, it is necessary to note that only 21% of the patients manifested that they were willing to accept any treatment if the doctor recommended it. The authors concluded that the idea that many patients have of

preventive treatment is determined by the way in which it is presented. These results indicate that many patients might not accept treatment even if the findings of published trials were presented in a clear and comprehensible way by physicians. In fact, communication of the potential effects (beneficial and harmful) of treatment to patients has special importance, particularly in primary prevention, where subjects are usually symptomatic and the benefits, if there are any, can only be expected in the long term. There are no studies in which, after informing patients about the potential benefits and drawbacks of the intervention, the probability of acceptance is measured in relation to the way in which this information is presented (RRR, ARR or NNT). In addition, it is necessary to incorporate results that have not been considered much to date and have only been recently incorporated in trials, such as measurements of the quality of life.

Finally, it would be very interesting to know if the active participation of patients in the process of therapeutic decision-making produces a benefit (increased satisfaction, better quality of life, etc.), how large this benefit is, and the mechanisms and factors that could explain this benefit (better compliance, better perception of the problem, etc). To date, only testimonial evidence sustains the hypothesis that the active participation of patients in therapeutic decision-making can improve the clinical results of intervention. On the other hand, there is fear that this participation can negatively affect the doctor-patient relation.

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