What Target for Guidelines: Uniformed or Tailored?

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A number of metaanalyses have shown that the benefit given by a treatment depends on the untreated risk as well as other patients’ characteristics, rather than being constant throughout the target population. Two of these metaanalyses will be reviewed later.

Further, epidemiologists have long shown, especially in the cardiovascular domain, that the risk of a given event is quite diverse among patients and healthy people according to the number of risk factors and their intensities. Thus, merely because of the arithmetic interaction (see below), the benefit will vary accordingly.

WHICH BENEFIT?

Here, a point should be made so as not to be confused. The benefit that has a good chance of best fulfilling patients’ wishes is the absolute benefit:

\[ \Delta = R_c - R_t, \]

where \( R_c \) is the untreated risk (ie, the risk estimated by the epidemiologists) and \( R_t \) the risk while receiving treatment. The only case where the absolute risk is constant over the range of \( R_c \) is when the effect model is additive:

\[ R_t = R_c - \Delta, \]

for any value of \( R_c \). So, we need a little more insight into the issue of effect model, so we can understand the point.

EFFECT MODEL

Definition  Let \( E \) = the outcome and \( R_c \) = the probability of it’s occurring during the length of time when the treatment is not given, referred to as the untreated risk. At a group level, it could be approximated by the observed incidence of the event in the control group of a clinical trial. The treated risk, \( R_t \), is the probability of the outcome associated with the treatment occurring in the same patients. An effect model is any expression that gives \( R_t \) as a function of \( R_c \) and covariate \( Y \) and that interacts with the treatment effect:

\[ R_t = f[R_c, Y]. \]

From this equation, one can derive algebraically or by computation any of the current indices of the size of the effect (1), eg, the risk ratio, \( R_t/R_c \), or the difference of risk, \( R_c - R_t \):

\[ I = g[R_c, Y] \quad [1]. \]

The Simplest Effect Models  The simplest effect models are linear, with only \( R_c \) as an explanatory variable. The full linear univariate model is:

\[ R_t = a \times R_c + b \quad [2]. \]

If, for instance, \( b > 0 \) and \( a < 1 \), the treatment has both a favorable effect, reducing the incidence of the outcome, and a hazardous effect, causing the outcome (see an example below). Slope \( a \) quantifies the favorable effect, and \( b \) is the constant risk of the hazardous effect during the same time. The overall net effect can be either favorable or hazardous, depending on the value of \( R \). \( S_0 \), the critical basal risk or the threshold risk, is given by \( S_0 = b/(1 - a) \). In a linear model, \( b \) is constant.
In addition to the full linear univariate model, two even simpler linear effect models are of interest. With the multiplicative model, \( b = 0 \), the treatment is consistently favorable and the size of the effect expressed as the risk ratio is proportional to \( R_c \) and constant over the range of the basal risk, whereas the risk difference increases linearly with \( R_c \). With the additive univariate linear model, \( a = 1 \), the size of the effect expressed as the risk difference does not depend on \( R_c(R_c - R_t = -b) \), whereas the risk ratio decreases when \( R_c \) increases. Note that the current metaanalytic techniques on fourfold tables assume either one of these simplest models.

**Examples of Varying Absolute Benefit**

**\( \beta \)-Blocking Agents in Postmyocardial Infarction Patients** In the mid-eighties, nine randomized trials of \( \beta \)-blocking agents (BB) in patients recovering from an acute myocardial infarction (MI) were performed, giving diverse, apparently inconsistent results. However, the overall effect computed across the trials with a metaanalysis was clear and quite consistent with the hypothesis laid down in the late sixties, ie, that such drugs could decrease mortality, especially sudden death, in these patients (although it later came out that the therapeutic model the trials were based on could not explain the decrease in the rate of reinfarction, which was unexpected). A review of the eligibility criteria and the description of the randomized patients showed that the studied population was rather at the low-risk side than the average post-MI patient. Because BB were known to impair left ventricular function in patients with borderline left ventricular failure or overt cardiac failure, and as the post-MI patients in the higher risk range are more likely to develop left ventricular failure, the question arose whether high risk post-MI patients would benefit or deteriorate from being prescribed BB. A metaanalysis performed on subgrouped summarized data obtained from the investigators of the nine trials has been the basis for the solution. The 1-year mortality rate was obtained for each subgroup, corresponding to a baseline variable assumed to be a secondary risk factor, for control and treated patients. A pooled or common odds ratio was computed from the two-by-two tables from each subgroup. The hypothesis of no interaction of the risk ratio with the untreated risk \( R_c \) was drawn from this analysis. Thus the effect model was assumed to be multiplicative and the only interaction was arithmetic. A trial was then performed on high risk patients to test the hypothesis. Its results were consistent with the model. Thus, for \( \beta \)-blockers in post-MI patients, the absolute benefit is:

\[
\Delta = R_c(1 - a).
\]

The absolute benefit increases linearly with the patient’s untreated risk.

**Class Ic Antiarrhythmics** A series of randomized trials with antiarrhythmics (AA) have been performed to test their effects on ventricular arrhythmias (VA) in post-MI patients. As these VA have been shown to predict sudden death, it was mistakenly thought that positive trials would give strong enough evidence for a beneficial effect of these drugs on mortality. This was later proved to be wrong when an increase in total
mortality and sudden death was demonstrated in patients receiving class Ic antiarrhythmics.\textsuperscript{6} A meta-analysis on the summarized data was performed for the 13 published trials.\textsuperscript{7} It gave poorly consistent findings when the results on mortality from various metaanalytic techniques were compared, with a low \( P \) value for heterogeneity with some, and nonstatistically significant heterogeneity with others. Exploration of the available data suggested that the apparent lack of coherence could result from an effect model that was neither multiplicative nor additive. A biologic interaction, due to a hazardous effect independent from the untreated risk, was assumed. The effect model derived from this assumption was a full linear univariate model, with the slope \( a \) for the favorable effect and \( b \) for the hazardous effect. It fit well the available data and gave a fair prediction of the results of a further trial. This model suggests that the therapy should not be given to patients with spontaneous risk of 1-year mortality \( < S_0 = 12.5\% \). In patients with \( Rc = 0 \), the 1-year mortality was estimated at \( 5.5\% \pm 3.1\% \) (\( P = .001 \) for the null hypothesis), a figure consistent with a finding from a metaanalysis of trials with similar drugs in patients at risk of recurrent atrial fibrillation with a very low 1-year mortality.\textsuperscript{8} However, the hypothesis that patients at higher risk would benefit from being prescribed AA has not been tested so far.

**WHAT ABOUT ANTIHYPERTENSIVE THERAPY?**

In mild hypertension, the risk of presenting with a stroke or myocardial infarction is low. Hence, many hypertensive patients might be given a treatment the burden of which exceeds the absolute benefit. Thus, we need a more precise definition of the therapy target population. To achieve this, a steering committee with the principal investigators of the primary prevention trials in hypertension was set up. A protocol was prepared for the pooling and quality control of the data, and for performance of the analyses. A contract that all agreed upon regarding publication policy and ownership of the common database was proposed to the steering committee.\textsuperscript{9} The first results suggest that the relative risk is constant over the various subgroups: gender, age, cardiovascular history at baseline.\textsuperscript{10,11} One can conclude that the effect model for the antihypertensive therapies tested in large-scale clinical trials, ie, diuretics and \( \beta \)-blockers, is a simple linear multiplicative model. Thus, for a given subject with high blood pressure, the major determinant of the absolute benefit is the basal risk of later cardiovascular events. The next step is to provide the prescribers with a workable, ie, simple to apply, algorithm able to predict the absolute risk, or tables, such as the Sheffield table for lipid-lowering treatment.\textsuperscript{12}

**CONCLUSION**

The reasoning and the examples mentioned here demonstrate that the absolute benefit, the most meaningful for patients, is not constant for many treatments under many conditions.\textsuperscript{13} It is not possible to foresee the size of the benefit for a given patient unless one can predict the patient’s untreated risk and knows the effect model.

Hence, guidelines for the treatment of hypertensive patients should be tailored to their actual untreated risk of occurrence of a major cardiovascular accident.

**REFERENCES**

