In the abstracts in this journal that describe effective treatments, we provide our readers with numbers that summarise their clinical effect. These include the number of patients you need to treat to prevent 1 adverse outcome (NNT) and both the absolute risk reduction (ARR) and relative risk reduction (RRR) in the occurrence of adverse outcomes achieved by active therapy. In this EBM Note, we explain these numbers for our readers and use them to begin a glossary of terms that will appear in each issue.

In the first issue of Evidence-Based Medicine, we presented the results of the Diabetes Control and Complications Trial (DCCT) (1) into the effect of intensive diabetes therapy on the development and progression of neuropathy. In that trial, confirmed neuropathy developed among 9.6% of patients randomly assigned to usual care (1 or 2 insulin injections/d to prevent glycaemic symptoms; we will call this rate “C” for “control”) and among 2.8% of patients randomly assigned to intensive therapy (insulin pump or > 3 injections/d; we call this rate “E” for experimental). This difference was statistically highly significant, but how might this treatment effect be expressed in terms of its clinical significance? The traditional measure of this effect is the proportion or “relative” risk reduction (abbreviated RRR in our journal), calculated as (C - E)/C. In this example, the RRR is (9.6% - 2.8%)/9.6% or 71%; intensive therapy reduced the risk for developing neuropathy by 71%.

Why not confine our description of the clinical significance of this result to the RRR? The reason is that the RRR fails to discriminate huge absolute treatment effects (10 times those observed in this trial) from those that are trivial (1/10 000 of those observed here). For example, if the rates of neuropathy were 10 times those observed in this trial, and a whopping 96% of control patients and 28% of intensively treated patients developed neuropathy, the RRR would remain unchanged: RRR = (96% - 28%)/96% or 71%. And if a trivial 0.00096% of control and 0.00028% of intensively treated patients developed neuropathy, the relative risk reduction is as before: RRR still = (0.00096% - 0.00028%)/0.00096% = 71%! This is because the RRR discards the underlying susceptibility (or “baseline risk”) of patients entering randomised trials; as a result, the RRR cannot discriminate huge risks and benefits from small ones.

In contrast to these nondiscriminating RRRs, the absolute differences in the rates of neuropathy between control and experimental patients (C - E) clearly do discriminate between these extremes, and this measure is called the absolute risk reduction or ARR. In the DCCT, the ARR or (C - E) = 9.6% - 2.8% = 6.8%; in the extremely high hypothetical example, in which 96% of control patients and 28% of intensively treated patients developed neuropathy, the ARR or (C - E) = 96% - 28% = 68%; in the extremely low hypothetical example, in which a trivial 0.00096% of control and 0.00028% of intensively treated patients developed neuropathy, the ARR or (C - E) = 0.00096% - 0.00028% = 0.00068%. These ARRs retain the underlying susceptibility of patients and provide more detailed information than RRRs. But, unlike RRRs that can be recalled as whole numbers, ARRs are decimals and are therefore difficult to remember and do not slip easily off the tongue at the bedside.

If, however, we divide the ARR into 1 (i.e., if we “invert” the ARR or “take its reciprocal” so that it becomes 1/ARR), we generate a very useful number because it represents the number of patients we need to treat (NNT) with the experimental therapy in order to prevent 1 bad outcome. In the DCCT, we would generate the number of persons with diabetes we would need to treat with the intensive regimen in order to prevent 1 from developing neuropathy. In the trial, the NNT is 1/ARR or 1/6.8% or 147; we usually round that number upward (in this case, to 15), and we now can say that for every 15 patients who are treated with the more intensive insulin regimen, 1 is prevented from developing diabetic neuropathy.

Is 15 a large or a small number of patients that need to be treated to prevent 1 bad outcome? As with many important matters in medicine, the answer has to do with clinical significance, not statistical significance. This NNT of 15 certainly is far smaller than the number of patients we would need to treat in the extremely low hypothetical example, in which 1/ARR becomes 1/0.00068%, or an NNT of more than 147 000, a figure so vast that we cannot imagine anyone judging it to be worth the effort. We can get a better idea by comparing this NNT of 15 with that for other interventions we are familiar with in medicine. In doing so, we add the dimension of the duration of therapy: in the DCCT, treatment continued for an average of 6.5 years, meaning that we need to treat about 15 persons with diabetes for about 6.5 years with an intensive insulin regimen to prevent 1 from developing neuropathy. How does this compare with other treatments, over other durations, for other conditions?

Beginning on an optimistic note, only about 20 patients with chest pain who appear to be having heart attacks need to be treated with streptokinase and aspirin to save a life at 5 weeks. On the other hand, about 70 elderly persons with hypertension need to
be treated for 5 years with antihypertensive drugs to save 1 life, about 100 men with no evidence of coronary heart disease need to be treated for 5 years with aspirin to prevent 1 heart attack, and about 10 patients with symptomatic moderate-to-severe carotid artery stenosis need to have endarterectomy to prevent 1 major or fatal stroke over the next 2 years. We think that the NNT to prevent 1 event is a very useful measure of the clinical effort we and our patients must expend to help them avoid bad outcomes of their illnesses. Accordingly, we will report NNTs in the “Main Results” sections of our abstracts whenever possible. NNTs will be accompanied by the actual event rates and their resultant P value and will be followed by their associated RRR.

Furthermore, because we are focusing here on the magnitude of the treatment effect rather than on the probability that we have drawn a false-positive conclusion that the treatment is at all effective (when it is not), we shall report confidence intervals (CIs) around the NNT, specifying the “limits” within which we can confidently state the true NNT lies (95% of the time). Readers who want to brush up on CIs can refer to an earlier editorial in our companion publication, ACP Journal Club (2), and we will also discuss them here in a future EBM Notebook.

Another useful feature of the NNT is the ease with which readers can convert it to NNTs for specific patients in their own practice by using some very simple arithmetic. All the reader needs to do is to estimate the susceptibility (sometimes called the “baseline risk”) of her own untreated patient relative to the average control patient in the trial report, and then express this estimate as a decimal fraction we will call “F” (if a reader judged her patient to be twice as susceptible as the average control patient in the trial, then F = 2); if her patient was only half as susceptible, then F = 0.5; and if the patient is as susceptible as the control patients in the trial, then F = 1) (3). If the treatment produces a constant RRR across the spectrum of susceptibilities, the NNT for her patient is simply the reported NNT divided by F. Going back to our intensive insulin example, if a reader’s patient was judged to have only half the susceptibility of patients in that trial, then F = 0.5 and NNT/F = 15/0.5 = 30; thus, 30 of these less susceptible patients would need to be treated for about 6.5 years with the intensive insulin regimen to prevent 1 from developing neuropathy.

This science of the art of extrapolating the results of published reports to individual patients is still in its infancy. We are just beginning to learn how to distinguish situations in which we can (usually with drug treatments) and cannot (sometimes with surgical treatments) assume constant RRRs over the ranges of susceptibilities we commonly encounter, and how to integrate this information with the rest of our clinical findings and clinical judgement. When this learning leads to important advances in our ability to extrapolate from trials to individual patients, we will report them here.

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References
On some clinically useful measures of the effects of treatment

Evid Based Med 1996 1: 37-38
doi: 10.1136/ebm.1996.1.37

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