Education and debate

The number needed to treat: a clinically useful measure of treatment effect

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The relative benefit of an active treatment over a control is usually expressed as the relative risk, the relative risk reduction, or the odds ratio. These measures are used extensively in both clinical and epidemiological investigations. For clinical decision making, however, it is more meaningful to use the measure "number needed to treat." This measure is calculated on the inverse of the absolute risk reduction. It has the advantage that it conveys both statistical and clinical significance to the doctor. Furthermore, it can be used to extrapolate published findings to a patient at an arbitrary specified baseline risk when the relative risk reduction associated with treatment is constant for all levels of risk.

More emphasis is now being put on effective use of biomedical literature to guide clinical treatment. As a result accessing, critically appraising, and incorporating the results of clinical investigations into clinical practice are becoming higher priorities for doctors and medical students.[1]

A pivotal step in translating clinical research into practice is the summarisation of data from randomised trials in terms of measures of effect that can be readily appreciated by doctors and other carers. Various measures of the effect of treatment are used in analysing results. Each measure has its own interpretation and statistical properties that make it suitable for some applications but perhaps not for others. We describe here a new measure referred to as number needed to treat[2] and a simple method of adopting this approach to individual patients at different levels of risk.

Measures of treatment effect

Consider a parallel group study in which patients are randomised to either an active treatment or a placebo control arm, are followed for a fixed amount of time, and are observed to experience a binary response to treatment (event/no event). We assume here that the events are adverse, and the objective is therefore to prevent them.

The effect of treatment is usually measured by comparing the probabilities of events in the two groups of patients. Point estimates of these measures are obtained by substituting the observed rate of events for the probabilities. For example, the absolute risk reduction is the difference in the probabilities of an event in the control and treatment groups and is estimated as the corresponding difference in the event rates. If the event rate in the treatment group is less than that in the control group this suggests a potential benefit from the active treatment. Similarly, if the event rate is greater in the treatment group than the control group (negative absolute risk reduction) the active treatment may be harmful. Before recommendations can be made regarding the

treatment more formal analyses of the treatment effect are needed to quantify the strength of evidence: this is done by tests of significance or confidence intervals.

Another approach to summarising effects of treatment is based on the relative risk. Relative risk is defined as the probability of an event in the active treatment group divided by the probability of an event in the control group. The relative risk can be conveniently estimated as the ratio of the corresponding event rates, with beneficial treatments giving relative risks below one. A related measure, called the relative risk reduction, is derived simply by subtracting the relative risk from one. On this scale a relative risk reduction of zero indicates no benefit or harm associated with the active treatment, whereas a relative risk reduction of one could indicate a "cure." The relative risk reduction can also be expressed as the absolute risk reduction divided by the probability of an event in the control arm and hence can be thought of as a standardised measure of the absolute risk reduction.

Another measure often used to summarise effects of treatment is the odds ratio. This is defined as the odds of an event in the active treatment group divided by the odds of an event in the control group. Though this measure has several statistical advantages and is used extensively in epidemiology, we will not pursue it here as it is not helpful in clinical decision making.

For some treatments and conditions the benefit of a specific treatment, as measured by the relative risk or the relative risk reduction, remains roughly constant over patient populations at varying baseline risk. In these cases relative measures appear attractive since a single estimate of treatment effect can be provided for a broad class of patients. On the other hand, it is often clinically important to consider the baseline (control) risk of an event before recommending treatment since for a given relative risk reduction, the expected absolute benefit of treatment could vary considerably as the baseline risk changes. For example, an estimated relative risk reduction of 50% might be statistically significant and clinically important for patients at moderate to high risk of a particular adverse event. However, for patients with a low probability of an event the risk reduction might not be sufficient to warrant the toxicity and cost of active treatment. This is the main criticism of relative measures of treatment effect for the purposes of clinical decision making.

Number needed to treat

Laupacis et al introduced an alternative approach to summarising the effect of treatment in terms of the number of patients a clinician needs to treat with a particular therapy to expect to prevent one adverse event.[2] The "number needed to treat" can be expressed as the reciprocal of the absolute risk reduction. In addition, a 95% confidence interval for the number needed to treat can be constructed simply by inverting and exchanging the limits of a 95% confidence interval for the absolute risk reduction. Though mathematically related to risk differences, the number needed to treat formulation is becoming widely used as a tool for therapeutic decision making[3] and bedside teaching[4] as it facilitates interpretation in terms of patients treated rather than the arguably less intuitive probabilities.

We use data from a recently published overview on the benefit of antihypertensive therapy for mildly and moderately hypertensive patients[5] to show the advantages (table). We divided studies in the overview into two groups: those in which all patients had a diastolic blood pressure of less than 110 mm Hg at entry and those in which all patients

had a diastolic blood pressure of less than 115 mm Hg at entry. The two groups of studies were mutually exclusive, although the second group of studies includes patients with diastolic blood pressure of less than 110 mm Hg. The table shows that for patients with moderate hypertension receiving placebo treatments about 20% would be expected to have a stroke over the next five years; this risk is reduced to 12% with antihypertensive drugs, generating an estimate of the absolute risk reduction of 0.20-0.12=0.08. The reciprocal of this number is about 13, implying that a doctor would need to treat about 13 moderately hypertensive patients for five years before he or she could expect to prevent one stroke.

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Calculation of risk reduction and numbers needed to be treated for
patients with hypertension (based on results of Collins et al⁵)
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------------------------------------------------------------------------
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                                           Stroke in 5 years
                   ------------------------------------------------------
Relative                        Absolute                    Number
                                         Control                   Active
risk reduction                  risk reduction      needed to treat
Hypertension                                     group   treatment group
(Pc-PA)/Pc    Pc-PA   1/(Pc-PA)
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------------------------------------------------------------------------
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Moderate (diastolic </=115 mm Hg)
 Event rate (P)                                     0.20             0.12
0.40                            0.08                   13
 Total No of patients                    16778     16898
Mild (diastolic </=110 mm Hg):
 Event rate (P)                                     0.015           0.009
0.40                            0.006                 167
 Total No of patients                    15165     15238
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The attractive feature of the number needed to treat analysis over methods based on measures of relative efficacy is seen if we compare moderately and mildly hypertensive patients. For both risk groups the relative risk reduction is 40%, suggesting that both groups should be treated with equal vigour. However, the estimate of the number needed to treat to prevent one stroke is 13 for moderately hypertensive patients and 167 for mildly hypertensive patients. The clinical recommendation is therefore likely to be different for these two groups.

Extrapolating to patients at different baseline risks

The numbers needed to treat method still presents a problem when applying the results of a published randomised trial in patients at one baseline risk to a particular patient at a different risk. For example, in the hypertension example suppose a particular patient had only half the baseline risk of stroke of the moderately hypertensive patients in the overview. Such a judgment is typically made by comparing the patient's clinical history with the characteristics of the study patients, as indicated by baseline variables and inclusion or exclusion criteria.

Until now, the published relative risk reduction has been applied to the individual patient's baseline risk. This assumes a constant relative risk reduction for varying baseline risks, as is the case in our example. The estimated relative risk reduction of 40% from the trial would be applied to the patient's hypothesised baseline risk of 0.10 (0.2x0.5), generating an estimated absolute risk reduction of 0.04. This number would then be inverted, resulting in a number needed to treat of 25. The process becomes even more laborious when it is necessary to calculate the 95% confidence interval around the relative risk reduction. This requires two additional calculations based on the confidence limits for the relative risk reduction.

When we used the number needed to treat method in decision making during ward rounds we found translating the results of published trials to individual patients at potentially different baseline risks was time consuming and that the results were sometimes incorrect. We therefore looked for a simpler method.

The process can be greatly simplified by comparing the baseline risk of an individual patient with that of the typical patient in the published trial. If the baseline risk of the individual patient is a factor f times the baseline risk of a typical study patient and the relative risk stays constant, the absolute risk reduction for the patient is scaled according to the same factor f. The estimated number needed to treat corresponding to patients at the revised baseline risk is therefore simply the study number needed to treat divided by f. Thus, in our example if a patient was judged to be at only half the baseline risk of the moderately hypertensive patients in the published trial f=0.5 and the corresponding number needed to treat is 12.5/0.5 or 25. Confidence intervals can be easily obtained by dividing the limits of the corresponding interval from the original study by the factor f. In the trial the 95% confidence interval for the absolute risk reduction in moderately hypertensive patients was (11.4 to 13.9). The corresponding interval for a patient at half the baseline risk is therefore (11.4/0.5 to 13.9/0.5)=(22.8 to 27.7).

This simplification of translating the results of published trials to individual patients allows easy and rapid consideration of questions such as "what if the patient's risk was a third or a quarter that of patients in the published trial?" The ability to perform these sensitivity analyses is important since the baseline risk is partly based on subjective clinical judgment.

In our example the assumption of a constant risk reduction is satisfied exactly. If we consider the baseline risk of mildly hypertensive patients as 0.015/0.200=0.075 times that of the moderately hypertensive patients, we obtain a number needed to treat of 1/(0.08x0.075)=167, the same value derived from the raw data. Though this is an extreme example the general approach has proved useful in a wide variety of clinical scenarios when a quick "adjusted number needed to treat" is required and departures from the assumption of constant relative risk reductions are expected to be minimal.

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