Australian and New Zealand Journal of Ophthalmology (1999) 27, 137–142

Review Article

Number needed to treat: A useful new method of assessing the magnitude of treatment effect and its application to the management of diabetic retinopathy*

Joseph A San Laureano, MB, BS,[1†] Esther M Briganti, FRACPI[2] and Deborah J Colville, FRACO[3]
[1]University of Melbourne, Department of Ophthalmology, East Melbourne, [2]Monash University, Department of Epidemiology and Preventive Medicine, Prahran and [3]Royal Children's Hospital, Ophthalmology Unit, Parkville, Victoria, Australia

Abstract

The magnitude of treatment effect from randomized controlled trials can be measured in various ways. The number needed to treat is a recently described measure that has been shown to offer several advantages in the clinical interpretation and application of reported treatment effects. It quantifies the number of patients that must be treated in order to prevent one patient from developing the specified outcome. The methods necessary to calculate traditional measures of treatment effect, as well as the number needed to treat, are outlined using the management of diabetic retinopathy as an example. The uses and limitations of the number needed to treat are also discussed.

Key words: clinical decision making, clinical epidemiology, diabetic retinopathy, number needed to treat, treatment effect.

Methods for Assessing the Effect of Treatment

Randomized controlled studies provide the most valid estimate of the effect of a new treatment compared with conventional or placebo treatment, both with regard to beneficial and harmful outcomes. The magnitude of the association between a treatment and an outcome can be expressed by a number of different measures when the outcome is dichotomous. These measures compare, in various ways, the observed rate of a particular outcome in the two treatment groups and convey different qualities with regards to the treatment effect.

Traditional measures include relative risk and relative risk reduction, which are measures of the strength of the association between treatment and outcome and absolute risk reduction, which is a measure of the actual magnitude of the association between treatment and outcome. The absolute risk reduction is the most relevant measure of treatment effect with regard to clinical decision making because it takes into account both the baseline risk and the magnitude of risk reduction. The number needed to treat is a recently described measure of treatment effect and is simply the reciprocal of the absolute risk reduction.[1] It has been shown to offer several advantages in the clinical interpretation of treatment effect size, which will be explored in the present paper.

Preventing Diabetic Retinopathy: An Important Ophthalmic Problem

We use data from the Diabetes Control and Complication Trial (DCCT) of the benefits and harm of intensive glycaemic control for the prevention of diabetic retinopathy to describe the properties of these measures as well as the methods used to calculate them, allowing the reader to calculate these values for any other study of interest.

The DCCT was a randomized controlled study designed to determine whether intensive treatment would affect the development and progression of vascular and neurological complications in patients with type 1 diabetes mellitus compared with conventional treatment.[2] Intensive treatment involved three or more insulin injections per day or continuous insulin infusion pump, frequent blood glucose monitoring and frequent physician, nurse and dietitian contact

■ *Correspondence:* Deborah J Colville, PO Box 210, Heidelberg, Victoria 3084, Australia. Email: dcolville@usa.net

*Presented at the Ophthalmic Alumni, July 1995, Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, Australia.

†Present address: Prince of Wales, Department of Ophthalmology, Randwick, NSW, Australia.

aiming for normoglycaemia. Conventional treatment involved one or two insulin injections per day, daily monitoring of blood or urine, standard diabetic education and dietary counselling and routine quarterly clinic visits with no specific goals with regard to glycaemic control. The study involved 1441 patients between the ages of 13 and 39 years; 726 patients with no diabetic retinopathy and a duration of diabetes of 1–5 years forming the primary prevention cohort and 715 patients with mild-to-moderate non-proliferative retinopathy and a duration of diabetes of 1–15 years forming the secondary prevention cohort. Ninety-five per cent of all scheduled examinations were achieved in this study. The mean glycosylated haemoglobin level over the 9 years of follow up was 9.1% with conventional treatment, compared with 7.2% with intensive treatment.

Assessment of diabetic retinopathy was by seven-field stereoscopic colour fundus photographs every 6 months. Fundus photographs were graded by blinded assessors according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.[3] Development of clinically important diabetic retinopathy was defined as the development of at least three steps from baseline on the ETDRS scale that was sustained for 6 months for the primary prevention cohort and progression of at least three steps on the ETDRS scale that was sustained for 6 months for the secondary prevention cohort.

Traditional Methods of Assessing the Effect of Treatment: Relative Risk, Relative Risk Reduction and Absolute Risk Reduction

Treatment effect can be described by the relative risk, which is the risk of the outcome occurring in patients receiving a new treatment (A) compared with the risk of the outcome with conventional or placebo treatment (B). The relative risk is calculated as A/B. A relative risk of 1 indicates no difference in effect between the two treatments. Efficacious new treatments give relative risks of < 1 and the smaller the relative risk, the more efficacious the new treatment. A new treatment that is less efficacious than conventional or placebo treatment gives a relative risk of > 1 and the larger the relative risk the less efficacious the new treatment.

A related measure is the relative risk reduction, which is defined as the percentage decrease in risk of the outcome with the new treatment compared with the risk in the conventional or placebo-treated group. The relative risk reduction is calculated as:

$$((B - A)/B) \times 100\%$$

or can be calculated as the complement of the relative risk and is expressed as a percentage (Appendix 1):

$$(1 - (A/B)) \times 100\%$$

A relative risk reduction of 0% indicates no difference in effect between the two treatments. A positive relative risk reduction indicates that the new treatment is more efficacious than conventional or placebo treatment; the greater the relative risk reduction, the more efficacious the new treatment, with a relative risk reduction of 100% indicating a cure. A negative relative risk reduction indicates that the new treatment is less efficacious than conventional or placebo treatment.

Based on the results of the primary prevention cohort of the DCCT, the proportion of patients with type 1 diabetes mellitus without diabetic retinopathy developing clinically important diabetic retinopathy over a period of 9 years with conventional treatment is 52.2%.[4] This can be reduced to 14.3% with intensive treatment. This represents a relative risk of 0.27 and a relative risk reduction of 73% with intensive treatment (Table 1).

However, the clinical impact and implications of treatment cannot be appreciated by the relative risk reduction,

Table 1. Primary and secondary prevention of clinically important diabetic retinopathy over 9 years

Clinically important diabetic retinopathy	Primary prevention cohort	Secondary prevention cohort
Intensive treatment (A)	0.143	0.140
Conventional treatment (B)	0.522	0.494
RR	0.27	0.28
RRR (%)	73	72
ARR (%)	37.9	35.4
NNT	2.6	2.8
NNT/year	24	25

Based on The Diabetes Control and Complications Trial Research Group.[4]

For the calculation of relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT), refer to formulae given in Appendix 1.

For the calculation of 95% confidence intervals for RRR, ARR and NNT, the number of patients in the primary prevention cohort receiving intensive treatment was 378, while the number receiving conventional treatment was 348.

given that it can be the same whether the risk with treatment decreases from 0.5 to 0.25 or from 0.05 to 0.025, in this case 50%. Therefore, before deciding whether the effect of a new treatment is clinically relevant, the baseline risk of an outcome with conventional or placebo treatment needs to considered (B). This is expressed as the absolute risk reduction and is calculated as (Appendix 1):

$$(B - A) \times 100$$

Based on the results of the primary prevention cohort of the DCCT, the baseline risk of developing clinically important diabetic retinopathy over 9 years is 52.2% and the risk with intensive treatment is 14.3%. Therefore, the absolute risk reduction is 37.9% with 9 years of intensive treatment (Table 1).

Number Needed To Treat: A Clinically Useful New Measure for Quantifying Treatment Effect

The clinical usefulness of the absolute risk reduction can be extended by the calculation of the number needed to treat, which is the reciprocal of the absolute risk reduction. This term describes how many people need to be treated for a specific period of time to prevent one additional outcome, if a new treatment is compared with conventional or placebo treatment. This calculation enables quantification of the treatment effect in a way that is more clinically useful and, therefore, more easily applicable with regard to decisions about the degree of treatment efficacy and willingness to prescribe the treatment by clinicians. Additionally, the effect of different treatments on the same outcome can be compared.

In order to standardize treatment effects that may be observed over different periods of time, an annual number needed to treat can be calculated by multiplying the number needed to treat by the duration of the study in years; however, the validity of this calculation is limited by the assumption of a constant effect of treatment over time.

With regard to the DCCT, intensive treatment for 9 years in 2.6 patients without retinopathy will prevent one additional patient developing clinically important diabetic retinopathy compared with conventional treatment. Assuming a constant effect of treatment over time, this equates to intensively treating 24 patients to prevent one additional patient progressing to clinically important diabetic retinopathy each year. However, this is not the case, given the more detailed information available regarding the effect of time on the impact of intensive treatment.

As can be seen from Table 2, the effect of intensive treatment on diabetic retinopathy is not linear. There is an initial harmful effect of intensive treatment that actually results in clinically important diabetic retinopathy developing in 0.7% of patients in the first year of treatment. Expressed more meaningfully, for every 143 patients undergoing intensive rather than conventional treatment, one will develop clinically important diabetic retinopathy in the first year of treatment. However, by the fourth year of treatment, one patient would have been prevented from developing clinically important diabetic retinopathy if 9.4 patients undergo intensive rather than conventional treatment for 4 years. Assuming an averaged effect of the 4 years of treatment, this would equate to intensively treating 38 patients annually. After 6 years of treatment, one patient would have been prevented from developing clinically important diabetic retinopathy with intensive treatment of 4.2 patients for 6 years. Again, assuming an averaged effect of the 6 years of treatment, this would equate to intensively treating 25 patients annually. The decreasing number of patients who need to be treated annually with increasing duration of treatment to prevent one developing clinically important of diabetic retinopathy reflects the fact that the full benefit of intensive treatment is not realized without long-term perseverance with treatment. In fact, the effect of intensive treatment is not statistically different to conventional treatment until after 4 years of treatment.

The relative risk, relative risk reduction, absolute risk reduction and number needed to treat for secondary prevention of diabetic retinopathy with intensive glycaemic control can also be seen in Table 1. Although it is apparent that a similar number of patients in the primary and secondary prevention cohorts need to be intensively treated to prevent one additional patient developing clinically important diabetic retinopathy, patients in the secondary prevention cohort already had mild-to-moderate retinopathy at baseline.

A similar application of these measures for other retinopathy outcomes is demonstrated in Table 3. From the secondary prevention cohort results, it can be seen that, with

Table 2. Effect of treatment interval on the primary prevention of clinically important diabetic retinopathy

Clinically important diabetic retinopathy	Treatment interval (years)			
	1	4	6	9
Intensive treatment (A)	0.020	0.035	0.113	0.143
Conventional treatment (B)	0.013	0.141	0.351	0.522
RR	1.54	0.25	0.32	0.27
RRR (5)	–54	75	68	73
ARR (%)	–0.7	10.6	23.8	37.9
NNT	–143	9.4	4.2	2.6
NNT/year	–143	38	25	24

Based on The Diabetes Control and Complications Trial Research Group.[4]

For the calculation of relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT), refer to formulae given in Appendix 1.

conventional treatment, 27% of patients will develop clinically significant macular oedema over 9 years. This risk can be reduced to 15% with intensive treatment. Given the absolute risk reduction of 12%, 8.3 patients need to be treated for 9 years, or 75 patients each year, to prevent one patient from developing macular oedema. Similarly, 39 patients each year require intensive treatment to prevent one patient from developing severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy.

But what of the fate of the other patients? The remaining number will either not respond to treatment or do not need it. Returning to the example of developing clinically significant macular oedema, eight patients need to be treated for 9 years to prevent one from developing macular oedema. Of the remaining seven patients, 27% will develop macular oedema because they did not responded to treatment (the same proportion as the conventional treatment group) and the remaining 73% will not develop macular oedema. Unfortunately, it is usually not possible to predict who will or will not develop an adverse outcome and who will or will not respond to treatment; therefore, everyone must be treated. For any given number needed to treat, the higher the baseline risk of an adverse outcome the greater the number of patients who will develop the adverse outcome despite treatment.

Number Needed to Treat: A Useful Method for Quantifying Harm as well as Benefit

The harmful effects of treatment can be quantified in a similar manner to the beneficial effects. As outlined previously, when the effect of a new treatment is to cause more outcomes than conventional or placebo treatment, then the relative risk is > 1 and the relative risk reduction, absolute risk reduction and number needed to treat are negative. Hypoglycaemia has been documented to be the most common adverse effect of intensive glycaemic control. After 9 years of treatment it was found that 73% of patients with intensive treatment developed at least one episode of severe hypoglycaemia compared with 40% undergoing conventional treatment.[5] As outlined in Table 4, for every 27 patients with intensive treatment one will suffer at least one severe episode of hypoglycaemia per year compared with conventional treatment. This allows the treatment-related benefit and harm to be compared.

Precision of Study Estimates

While the calculation of number needed to treat is useful for interpreting the effectiveness or harm of particular treatments, it provides only a point estimate of the treatment effect based on the randomized controlled study from which it is derived. The degree of uncertainty in this point estimate is given by a confidence interval (CI). Ninety-five per cent CI can be calculated for relative risk reductions, absolute risk reductions and number needed to treat, as outlined in Appendix 2.[6] The 95% CI will not include 1 for the relative risk reduction, 0 for the absolute risk reduction or infinity for the number needed to treat when the treatment effect is statistically significant at the 5% level. The interpretation of the 95% CI of the number needed to treat when the treatment effect is not statistically significant, that is, when the 95% CI of the absolute risk reduction includes 0, is problematic because such a CI is discontinuous and centred on infinity. This issue has been discussed in greater detail elsewhere.[7]

Based on the formulae given in Appendix 2 and the results from the primary prevention cohort given in Table 1 for the development of clinically important diabetic retinopathy over 9 years using intensive compared with conventional treatment, the 95% CI for relative risk reduction, absolute risk reduction and for the number needed to treat are 61–85%, 31.7–44.1% and 2.3–3.2, respectively. The 95% CI for the number needed to treat per year is 21–29.

Table 3. Prevention of macular oedema and severe non-proliferative or proliferative retinopathy retinopathy outcomes over 9 years

	Macular oedema	Severe NPDR or PDR
Intensive treatment (A)	0.15	0.09
Conventional treatment (B)	0.27	0.32
RR	0.56	0.28
RRR (%)	44	72
ARR (%)	12	23
NNT	8.3	4.3
NNT/year	75	39

Based on The Diabetes Control and Complications Trial Research Group.[4]

For the calculation of relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT), refer to formulae given in Appendix 1.

NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4. Serious hypoglycaemia

Serious hypoglycaemia over 9 years	Entire cohort
Intensive treatment (A)	0.73
Conventional treatment (B)	0.40
RR	1.83
RRR (%)	–83
ARR (%)	–33
NNT	–3
NNT/year	–27

Based on The Diabetes Control and Complications Trial Research Group.[5]

For the calculation of relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT), refer to formulae given in Appendix 1.

Table 5. Prevention of visual loss with photocoagulation for patients with macular oedema and mild-to-moderate diabetic retinopathy

Visual loss of three or more lines	Treatment duration (years) 1	2	3
Immediate focal (A)	0.05	0.07	0.12
Deferred focal (B)	0.08	0.16	0.24
RR	0.63	0.44	0.50
RRR (%)	37	56	50
ARR (%)	3	9	12
NNT	33.3	11.1	8.3
NNT/year	33	22	25

Based on Early Treatment Diabetic Retinopathy Study Research Group.[11]

For the calculation of relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT), refer to formulae given in Appendix 1.

Discussion

As has been outlined, a number of measures are available to describe the magnitude of treatment effect. The measures can be relative or absolute and, as such, convey very different meaning. The relative risk and relative risk reduction give a quantitative sense of the treatment effect in proportional terms, but do not reflect the magnitude of effect on an absolute scale. The absolute risk reduction and number needed to treat incorporate both the baseline risk and the magnitude of the risk reduction and, therefore, provide information as to the clinical usefulness of treatments.

It has been shown that a clinician's perception of the magnitude of treatment effect is strongly influenced by the measurement that is used to report it.[8–10] The reporting of relative risk reduction has a positive influence on the perception of the magnitude of treatment effect and the likelihood of clinicians prescribing the treatment. This most likely reflects the apparent overstated effect of treatment when study results are presented as a relative risk reduction.

The type of analysis outlined in the present paper allows us to more clearly see what degree of effort is required with any particular treatment to achieve a particular outcome with our patients. A similar number of patients with type 1 diabetes need to be intensively treated each year to prevent the development (number needed to treat: 24) or progression (number needed to treat: 25) of clinically important diabetic retinopathy. More patients with diabetic retinopathy need to be intensively treated to prevent the further development of severe non-proliferative or proliferative diabetic retinopathy (number needed to treat: 39) or macular oedema (number needed to treat: 75), reflecting the lower baseline risk and smaller risk reduction achieved with intensive treatment for these complications. Consideration of potential harm from intensive treatment indicates that for every 27 patients treated each year with intensive treatment, one will develop at least one episode of serious hypoglycaemia.

The magnitude of benefit of immediate compared with deferred photocoagulation for patients with macular oedema and mild-to-moderate diabetic retinopathy in the prevention of visual loss of three or more lines is outlined in Table 5 as an additional example of an important ophthalmic problem.[11]

The usefulness of the number needed to treat method with regard to the application of reported treatment effects from randomized controlled studies to clinical practice has been demonstrated in the present paper.

References

1. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N. Engl. J. Med.* 1988; 318: 1728–33.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 1993; 329: 977–86.
3. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: An extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology* 1991; 98: 786–806.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial. *Arch. Ophthalmol.* 1995; 113: 36–51.
5. The Diabetes Control and Complications Trial Research Group. Hypoglycaemia in the Diabetes Control and Complications Trial. *Diabetes* 1997; 46: 271–86.
6. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*, 2nd edn. Boston, MA: Little Brown & Co. 1991.
7. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998; 317: 1309–12.
8. Forrow L, Taylor WC, Arnold RM. Absolutely relative: How research results are summarized can affect treatment decisions. *Am. J. Med.* 1992; 92: 121–4.
9. Naylor CD, Chen E, Strauss B. Measured enthusiasm: Does the method of reporting trial results alter the perception of therapeutic effectiveness? *Ann. Intern. Med.* 1992; 117: 916–21.
10. Bucher HC, Weinbacher M, Gyr K. Influence of method of reporting study results on decision of physicians to prescribe drugs to lower cholesterol concentration. *BMJ* 1994; 309: 761–76.
11. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS report number 1. *Arch. Ophthalmol.* 1985; 103: 1796–806.

Appendix 1

Table A1. Calculation of measures of treatment effect

B, proportion of patients in the control group with an event
A, proportion of patients in the treatment group with an event

RR, relative risk: A/B
RRR, relative risk reduction:

$$((B - A)/B) \times 100\% \text{ or } (1 - (A/B)) \times 100\%$$

ARR, absolute risk reduction:

$$(B - A) \times 100\%$$

NNT, number needed to treat:

$$1/(B - A) \text{ or } 100\%/ARR$$

Appendix 2

Table A2. Calculation of 95% confidence intervals

B, proportion of patients in the control group with an event
A, proportion of patients in the treatment group with an event
NB, number of patients in the control group
NA, number of patients in the treatment group
D, duration of treatment

$$X = (B \times (1 - B)/NB) + (A \times (1 - A)/NA)$$

95% CI for RRR (RRR_{lower}, RRR_{upper}):

$$((B - A) \pm 1.96\sqrt{X/B}) \times 100\%$$

95% CI for ARR (ARR_{lower}, ARR_{upper}):

$$((B - A) \pm 1.96\sqrt{X}) \times 100\%$$

95% CI for NNT (NNT_{lower}, NNT_{upper}):

$$(1/ARR_{upper}, 1/ARR_{lower})$$

95% CI for the NNT/year:

$$(NNT_{lower} \times D, NNT_{upper} \times D)$$

CI, confidence interval; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat.