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Quantifying treatment effect: relative and absolute measures in clinical research

Alberto Maino,[1,2] Lorenza Bertù,[3] Alessandro Squizzato,[4,5] Paola Piccolo,[6] Fulvio Pomero[7]

[1]Internal Medicine Unit, Santa Chiara Hospital, Azienda Sanitaria Universitaria Integrata del Trentino (ASUIT), Trento; [2]Center for Medical Sciences, University of Trento; [3]Department of Medicine and Surgery, University of Insubria, Varese; [4]Internal Medicine Unit, Sant'Anna Hospital, ASST Lariana, S. Fermo Della Battaglia, Como; [5]Research Center on Thromboembolic Disorders and Antithrombotic Therapies, University of Insubria, Como; [6]Internal Medicine Unit, Ospedale Isola - Tiberina Gemlli Isola, Rome; [7]Internal Medicine Unit, Ospedale Michele e Pietro Ferrero, Verduno (CN), Italy

Correspondence: Alberto Maino, Center for Medical Sciences, University of Trento, Via S. Maria Maddalena, 1 - 38122 Trento, Italy.
Tel.: +39 0461 283100. E-mail: alberto.maino@unitn.tn.it

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Abstract
Quantifying the effect of treatment is crucial for clinical decision-making. Effect measures can be expressed in absolute terms, such as risk difference, number needed to treat, or number needed to harm, or in relative terms, including risk ratio, odds ratio, and incidence rate ratio. Although all are derived from the same data, they provide different perspectives: relative measures capture proportional changes, while absolute measures translate these into clinically meaningful terms.
Confidence intervals (CIs) are essential to assess the precision of these estimates and to evaluate their statistical significance and potential clinical relevance.
In this methodological note, we illustrate the use of these measures with examples from studies on venous thromboembolism, a clinical field where both benefits and risks of anticoagulant therapy (*i.e.*, thrombosis and bleeding) must be carefully balanced.
Clinicians and researchers should be aware of the strengths and limitations of each measure. A balanced interpretation, integrating absolute and relative metrics together with their CIs, is central to properly assessing treatment effects and to support evidence-based decision-making.

Introduction

Quantitative measures of treatment effect represent a key step in translating a research question into interpretable clinical evidence.[1] Clinicians must therefore understand several statistical measures to properly evaluate pharmacological and non-pharmacological interventions, beyond simply assessing statistical significance.[2,3]

Effect measures can be broadly categorised as (Figure 1): i) absolute measures [*e.g.*, risk difference (RD), number needed to treat (NNT)], which provide a direct estimate of the benefit or harm in absolute terms; ii) relative measures [*e.g.*, relative risk (RR), odds ratio (OR)], which express the effect as a ratio.

Both estimates are informative: absolute measures are particularly useful in clinical practice and patient communication, while relative measures are commonly used in research and express effects in relative terms.

The way in which results are expressed may strongly influence their interpretation, the perceived magnitude of benefit, and ultimately therapeutic choices. Although all these measures derive from the same underlying data, they offer different perspectives. Relative measures highlight proportional changes, often emphasising statistical benefit, whereas absolute measures contextualise the impact in clinical, patient-centred terms. This distinction is especially relevant in several medical conditions, such as venous thromboembolism (VTE), where baseline event rates may vary widely and influence absolute benefit.

The aim of this methodological note is to illustrate how to compute and interpret RD, NNT, RR, and OR, using examples from VTE prevention and treatment, and to discuss their complementary roles in clinical research and practice.

Absolute measures of effect

Risk difference

The RD represents the difference between the incidence proportion of a disease/event (risk) in the control group and the incidence proportion of the same outcome in the treated group.

RD = risk(*control*) − risk(*treatment)*

Therefore, when:

- RD>0 → fewer events with treatment (benefit), absolute risk reduction.
- RD<0 → more events with treatment (harm), absolute risk increase.

Alternative definitions are also used in the literature, where RD is calculated as treatment minus control. In this case, the sign determines whether the estimate reflects absolute risk reduction or increase.

Number needed to treat and number needed to harm

The NNT indicates the number of patients who need to be treated to prevent one additional adverse event. It can be calculated as the inverse of the absolute RD:

$$NNT = \frac{1}{RD}$$

The ideal NNT for a given treatment is 1. In fact, an NNT of 1 means that all treated individuals experienced a favorable outcome (*i.e.*, no events; absolute risk = 0), whereas all untreated individuals experienced the adverse outcome in question (*i.e.*, absolute risk = 100%).

When the treatment increases the risk of an adverse event, the concept is the same but expressed as the number needed to harm (NNH).

Absolute measures directly quantify the benefit or harm in practical terms, which is particularly relevant for clinical decision-making and patient communication. Importantly, NNT and NNH depend strongly on baseline risk and should be interpreted within the clinical context. Confidence intervals (CIs) around NNT/NNH can also be reported and provide information on the precision of these estimates. The AVERT trial showed that apixaban reduced thromboembolic events but increased major bleeding.[4] In absolute terms, apixaban reduced the risk of VTE by 6% compared to placebo, corresponding to an NNT of 17 to prevent one event, while increasing major bleeding by 1.7%, corresponding to an NNH of 59 (Table 1).
This example illustrates how absolute measures can reveal the clinical trade-off between efficacy and safety. Importantly, even when a relative measure appears clinically meaningful, the corresponding absolute measures may differ substantially because they depend strongly on the baseline risk of the population under study. For instance, a treatment associated with a 50% RR reduction for recurrent VTE may result in a very low NNT in cancer patients (where baseline VTE risk is high), but a much higher NNT in patients with provoked VTE after surgery (where baseline risk is low).

Relative measures of effect

Relative risk

The RR or risk ratio is the ratio of the incidence proportion of the event (risk) in the treatment *vs.* the control group:

$$RR = \frac{Risk\ (treatment)}{Risk\ (control)}$$

Therefore, when:
- RR=1: no difference.
- RR<1: reduced risk with treatment.
- RR>1: increased risk with treatment.

In the AVERT study, VTE occurred in 4.2% of patients receiving apixaban *vs.* 10.2% with placebo at 180 days; the RR is therefore 0.41, corresponding to a 59% RR reduction (Table 2). For major bleeding, the risk was 3.5% in patients taking apixaban and 1.8% in the placebo group, corresponding to an RR of 1.91, indicating almost a doubling of bleeding risk with apixaban.

Hazard ratio

In time-to-event analyses, results are often expressed as a hazard ratio (HR), which compares the instantaneous rate (hazard) of experiencing an event at any given time between two groups. Unlike the RR, which compares cumulative event probabilities at the end of follow-up, the HR incorporates information on when events occur and accounts for censoring, that is, for participants who are no longer observed or at risk before the outcome occurs due to study end, loss to follow-up, competing events such as death, or other reasons. When follow-up is short, the HR is usually close to the RR. Conversely, as follow-up extends, differences in event timing, censoring, and competing events may cause the two measures to diverge. These measures are conceptually distinct, as the HR reflects the instantaneous hazard over time, whereas the RR compares cumulative risks at a fixed time point. In the AVERT study, the HR for VTE with apixaban *vs.* placebo was 0.41, corresponding to a similar RR of 0.41 based on 180-day risks (4.2% *vs.* 10.2%, Table 2). In studies with longer follow-up or higher mortality, where cumulative RRs are used to estimate the occurrence of recurrent VTE, the HR may differ substantially from the RR, as the passage of time and competing risks modify the population

at risk. A clear example comes from the INSPIRE collaboration, which pooled the WARFASA and ASPIRE trials and followed patients for up to four years after discontinuation of anticoagulation.[5] Acetylsalicylic acid reduced recurrent VTE with an HR of 0.68, corresponding to a cumulative RR of 0.73 (14.8% *vs.* 20.3%) at the end of follow-up. This modest but tangible difference illustrates how longer observation periods and competing risks can influence effect estimates, emphasizing that HR and RR describe related but distinct dimensions of treatment effect over time.

Incidence rate ratio

When studies report outcomes as incidence rates (IR, events per person-time), the appropriate relative measure is the incidence rate ratio (IRR):

$$IRR = \frac{IR\ control}{IR\ treatment}$$

For example, in the CLOT trial the recurrence rate of thrombosis in patients with cancer-associated VTE was lower with dalteparin than with warfarin (9% *vs.* 17% at 6 months, corresponding to 18 *vs.* 34 events per 100 patient-years), yielding an IRR of about 0.53.[6]

IRRs are particularly useful in observational cohort studies (*e.g.*, the RIETE registry of VTE patients) or when follow-up duration is highly variable, because they account for time at risk. Although pivotal trials on direct oral anticoagulants in VTE (*i.e.*, AMPLIFY, AVERT, and EINSTEIN study) mainly reported cumulative risks and HRs, the IRR provides a complementary approach when person-time denominators are available.[4,7-9]

Odds ratio

The odds are another way of representing probability, often familiar to gamblers. For example, when rolling a die, the probability of getting a six is 1/6 (17%). The odds are expressed as 1 chance of success to 5 chances of failure, that is, 1:5. More generally, odds are calculated as the probability of an event divided by the probability of no event.

In epidemiology, the OR is used to compare the odds of exposure in cases relative to controls in case–control studies. It can be calculated from a standard 2×2 table:

	Exposed	**Unexposed**	**Total**
Cases	a	b	a+b
Controls	c	d	c+d
Total	a+c	b+d	N

The formula is: $OR = \frac{a/b}{c/d} = \frac{a\ X\ d}{b\ X\ c}$

A clinical example comes from the MEGA study, which investigated if cancer was a risk factor for VTE.[10] Among 3220 cases with VTE and 2913 controls, 242 cases and 50 controls had a cancer diagnosis (within 6 months).

	Cancer (exposed)	**No cancer (unexposed)**	**Total**
Cases (VTE)	a=242	b=2978	3220
Controls	c=50	d=2863	2913

- Odds of cancer among cases = a/b = 242/2978 = 0.081
- Odds of cancer among controls = c/d = 50/2863 = 0.017
- OR = (242×2863)/(2978×50) = 0.081/0.017 = 4.3 (95% CI 3.5-5.3)

Therefore**,** patients with a recent malignancy diagnosis had more than fourfold higher odds of developing VTE compared with those without cancer. The OR is the correct measure in the case–control design because it is invariant to the number of controls sampled per case. However, the OR is also commonly used in other settings, particularly in logistic regression models and in certain cohort or cross-sectional analyses. When the disease is rare, the OR approximates the RR; when the disease is common, it may overestimate the magnitude of the association compared with the RR and should therefore be interpreted with caution, particularly outside case–control settings.

Confidence interval

Effect measures are generally accompanied by a measure of precision: the CI. In the AVERT study, the RR for VTE with apixaban versus placebo was 0.41, with a 95% CI of 0.26-0.65. The concept of the CI can be explained as follows: if we were to repeatedly draw samples of the same size as in the AVERT study from the target population, and calculate the effect estimate in each sample, we would obtain slightly different results. The 95% CI represents the range of values compatible with the observed data. Under repeated sampling, 95% of such intervals would include the true effect. Importantly, the CI provides information not only on statistical significance, but also on the precision and potential clinical relevance of the estimate. From a statistical standpoint, an effect is considered significant (*i.e.*, $p<0.05$) if the 95% CI does not include the null value (1.0 for relative measures such as RR or OR). In the AVERT study, the RR of 0.41 (95% CI 0.26-0.65) for VTE was statistically significant, while the RR of 1.94 (95% CI 1.01-3.95) for major bleeding narrowly excluded 1.0, suggesting an increased bleeding risk with apixaban that was borderline in statistical terms.

A different situation can be observed in the CASSINI trial, which evaluated rivaroxaban versus placebo for thromboprophylaxis in ambulatory cancer patients at high risk of VTE.[11] The primary endpoint occurred in 6.0% of patients on rivaroxaban and in 8.8% of those on placebo, yielding a RR of 0.66 with a 95% CI of 0.40-1.09. Although the point estimate suggested a 34% RR reduction, the CI included 1.0. This means that, with 95% probability, the true effect could range from a 60% reduction to a 9% increase in risk. As the CI crossed 1.0, the result was not statistically significant ($p=0.10$).

The width of the confidence interval depends on the sample size and the number of observed events: studies with fewer participants and events yield wider CIs and therefore greater uncertainty, whereas larger trials produce narrower and more precise estimates. A further contribution comes from the intrinsic variability of the data, that is, how dispersed the observed event proportions are around their expected values, and from the selected confidence level, since higher confidence levels imply a larger margin of error. Importantly, statistical significance does not necessarily imply clinical relevance. A small but statistically significant effect may have little impact in practice, whereas a non-significant result with a wide CI may still suggest a clinically meaningful difference that the study was simply underpowered to detect.

CIs provide essential information on the precision, direction, and potential clinical importance of an observed effect, helping to distinguish between lack of effect and lack of statistical power.

Conclusions

Effect measures provide complementary perspectives on the same data. Relative measures such as the RR and OR are useful to quantify proportional changes and are standard in randomized trials and case–control studies, respectively. Absolute measures such as the RD, NNT, or NNH translate these results into more clinical terms for clinical decision-making. The CI is essential to interpret the precision of these estimates considering the random variation.

Examples from VTE trials and case–control studies highlight how the choice of effect measure may strongly influence interpretation. A favorable relative reduction may correspond to a modest absolute benefit if the baseline risk is low, while in high-risk populations the same relative effect yields a much lower NNT. Similarly, the OR, while indispensable in case–control designs, may overstate associations when outcomes are common.

Clinicians and researchers should therefore be aware of the strengths and limitations of each effect measure. A balanced interpretation that integrates relative and absolute measures, along with their confidence intervals, is crucial to translate evidence into meaningful patient care and to support evidence-based clinical decision-making.

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Table 1. Absolute measures of treatment effect in the AVERT trial (apixaban *vs.* placebo, incidence proportions at 180 days).

Endpoint	Apixaban	Placebo	Risk difference (ARR/ARI)	NNT/NNH
VTE	4.2%	10.2%	6.0% (ARR)	17 (NNT)
Major bleeding	3.5%	1.8%	-1.7% (ARI)	59 (NNH)

VTE, venous thromboembolism; NNT, number needed to treat; NNH, number needed to harm; ARR, absolute risk reduction; ARI, absolute risk increase. ARR and corresponding NNT are reported for VTE. ARI and NNH are reported for major bleeding. Data are derived from the AVERT trial.

Table 2. Relative measures of effect in the AVERT trial (apixaban *vs.* placebo, events at 180 days).

Endpoint	Apixaban (events/N)	Placebo (events/N)	Risk apixaban	Risk placebo	RR	HR (95% CI)
VTE	12/288	28/275	4.2%	10.2%	0.41	0.41 (0.26-0.65)
Major bleeding	10/288	5/275	3.5%	1.8%	1.91	2.00 (1.01-3.95)

VTE, venous thromboembolism; RR, relative risk; HR, hazard ratio; CI, confidence interval. RR, odds ratio, and HR (HR, from trial report) are shown for VTE and major bleeding.

Absolute Measures	Relative Measures
Risk difference (RD)	Risk Ratio (RR)
Number Needed to Treat (NNT)	Odds Ratio (OR)
Number Needed to Harm (NNH)	Hazard Ratio (HR)
	Incidence Rate Ratio (IRR)

Figure 1. Absolute and relative measures of treatment effect.