



Editorial

Beyond Relative Risk: A Methodological Framework for Interpreting Measures of Effect and Improving Data Presentation in Randomized Controlled Trials (RCTs)

Giovanni Tripepi ^{1,*}, Jolanta Malyszko ² , Michel Jadoul ³ and Francesco Locatelli ^{4,5}

¹ Section of Clinical Epidemiology and Biostatistics, Institute of Clinical Physiology, 89132 Reggio Calabria, Italy

² Department of Nephrology, Dialysis and Internal Medicine, Medical University of Warsaw, 02-091 Warsaw, Poland; jmalyszko@gmail.com

³ Division of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 1200 Brussels, Belgium; michel.jadoul@saintluc.uclouvain.be

⁴ Dipartimento di Scienze Cliniche e di Comunità, Dipartimento di Eccellenza, University of Milan, 20133 Milan, Italy; francesco.locatelli2210@outlook.it

⁵ Clinical and Experimental Medicine PhD Program, Azienda Unità Sanitaria Locale-Istituto di Ricovero e Cura a Carattere Scientifico di Reggio Emilia, Università di Modena and Reggio Emilia, 41100 Modena, Italy

* Correspondence: giovanniluigi.tripepi@cnr.it

Abstract

Randomized controlled trials (RCTs) are the gold standard for evaluating the efficacy and safety of medical interventions. However, the interpretation of their results is often obscured by an overreliance on relative measures of effect, such as relative risk reduction (RRR) and hazard ratios (HRs). While statistically robust, these measures may mislead clinicians and patients when used in isolation. This article provides a methodological framework for the comprehensive interpretation of treatment effects in RCTs, emphasizing the importance of integrating absolute measures such as absolute risk reduction (ARR), number needed to treat (NNT), annualized NNT (aNNT), and number needed to harm (NNH). Additionally, we explore the conceptual differences between risk-based and rate-based measures, the clinical implications of time-to-event analyses, and the utility of composite metrics such as the likelihood of being helped or harmed (LHH). By adopting a multidimensional approach to effect estimation, researchers and clinicians can enhance the translation of statistical findings into meaningful clinical decisions. This approach also facilitates communication with patients.

1. Introduction

On 2 March 2026, a round table held at the MDPI headquarters in Basel, Switzerland (St. Alban-Anlage 66), brought together Prof. Francesco Locatelli, Prof. Jolanta Małyszko, Prof. Michel Jadoul, and Dr. Giovanni Tripepi to discuss key methodological issues related to the presentation and interpretation of data from randomized clinical trials (RCTs). These issues were originally raised in the Editorial by Prof. V.M. Campese entitled “Truth and Pitfalls of Evidence-Based Medicine” [1], and provided the conceptual framework for the present paper.

RCTs are central to evidence-based medicine, providing high-quality data on the efficacy and safety of interventions. Despite their methodological rigor, the way results are reported and interpreted often limits their applicability and usability in everyday clinical



Received: 8 April 2026

Accepted: 13 April 2026

Published: 20 April 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

practice. A persistent issue is the emphasis on relative measures of effect, particularly relative risk (RR) and hazard ratios (HR), without sufficient consideration of absolute measures. Relative measures are appealing because they tend to magnify perceived treatment benefits. However, they do not convey the actual magnitude of benefit or harm experienced by patients. This disconnect can lead to misinterpretation, suboptimal decision-making, and even ethical concerns when trial results are translated into clinical practice. This article examines the key effect measures used in RCTs, highlighting their strengths, limitations, and appropriate interpretation.

2. Relative Measures of Effect: Strengths and Limitations

Risk Ratio and Hazard Ratio

We can interpret the HR in much the same way as the incidence rate ratio (IRR). A clear way to understand this is through an example using IRR calculations. Consider a RCT evaluating the effect of a hypothetical drug Y on 2-year mortality in patients with chronic kidney disease (CKD). For simplicity, suppose there are six patients in the treatment group and six in the control group. Over the 2-year follow-up period, in the control group, one patient was lost to follow-up after 1 year, one patient died at 8 months, and the remaining four patients completed the study. In the treatment group, one patient was lost after 18 months, one patient died at 24 months, and the other four completed the follow-up. If we calculate the risk (probability) of death in each group, both the control and treatment arms have one death out of six patients ($1/6 = 0.17$ or 17%). This gives a risk ratio between the two arms of 1, suggesting no difference between groups. However, this measure does not account for the timing of the deaths—the death in the treatment group occurred later than in the control group. To incorporate time, we calculate incidence rates based on person-time. In the control group, the total person-time is approximately 9.7 person-years ($12 + 8 + 24 + 24 + 24 + 24 = 116$ person-months $\rightarrow$ 9.7 person-years), giving an incidence rate of about $1/9.7 = 0.10$ deaths per person-year (or 10 death per 100 person-years). In the treatment group, the total person-time is 11.5 person-years ($18 + 24 + 24 + 24 + 24 + 24 = 138$ person-months $\rightarrow$ 11.5 person-years), yielding an incidence rate of $1/11.5 = 0.087$ deaths per person-year (or 8.7 per 100 person-years). These rates show that deaths occurred earlier in the control group, reflected by the higher incidence rate compared to the treatment group. The IRR is calculated as $0.087/0.10 = 0.87$. On the basis of an IRR of 0.87, we can state that the incidence rate of death is 13% lower in the active arm compared to the control arm of the trial, implying that the probability of death occurring first is 13% lower for patients in the active arm than for those in the control arm. Thus, we cannot state that the new treatment would provide 13% fewer deaths over 2 year as compared to the control group. Hazard ratios are often misinterpreted as relative risks. However, they are not directly interchangeable. HRs are typically farther from 1 than RRs because they capture time-dependent differences in event occurrence. For instance, if events occur earlier in the control group but later in the treatment group, the HR will reflect this temporal shift, while the RR (calculated by using cumulative risks) will average it out. As a result, relying solely on HRs may overstate the clinical benefit of an intervention.

3. Absolute Measures: Bringing Results to the Bedside

3.1. Absolute Risk Reduction (ARR), Number Needed to Treat (NNT), and Number Needed to Harm (NNH)

ARR is defined as the difference in risk between control and treatment groups:

$$ARR = Risk_{control} - Risk_{treatment}$$

Unlike relative measures, ARR provides a direct estimate of how many events (as a percentage) are prevented by the intervention over a given time period. It is essential for understanding the real-world impact of treatment and can be used to calculate the number needed to treat (NNT) [1,2].

The NNT is the reciprocal of ARR (when ARR is expressed as a fraction):

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

NNT is equal to 100 divided by ARR only when ARR is expressed as a percentage. NNT represents the number of patients who must be treated to prevent one additional adverse event over a specific time period. Consider a RCT comparing Treatment A with Treatment B for the prevention of death over 1 year period. The risk of mortality was 20% in the control group and 10% in the intervention group. This corresponds to an absolute risk reduction of 10 percentage points, yielding a NNT of 10 (i.e., $100/10 = 10$). In practical terms, this indicates that treating 10 patients with A instead of B would prevent one additional death over the study period (1 year). For translation to clinical practice, these results can be expressed at the bedside by conveying absolute risks: among 100 patients similar to the individual under consideration, approximately 20 deaths would be expected with Treatment B compared to 10 with Treatment A, corresponding to 10 fewer deaths per 100 treated. Presenting both the NNT and the absolute risk reduction facilitates interpretation by clinicians while allowing patients to better understand the magnitude of benefit in concrete terms. Thus, the NNT together with the absolute risk translate statistical findings into a clinically meaningful metric. The NNT should be presented together with its 95% confidence interval (95% CI) [3]. It is important to emphasize that ARR and NNT must always be contextualized and interpreted with attention when applied to individual patients [4]. Finally, it is important to remark that the NNT is highly dependent on baseline risk. Two trials with identical relative risk reductions (or IRR) can yield very different NNTs if the underlying (baseline) risk differs. Therefore, comparisons of NNT across studies can be useful only when baseline risks are similar.

Since no treatment is without risk, evaluating adverse effects is just as important as assessing benefits. The number needed to harm (NNH) is a metric used to quantify a treatment's safety. It is calculated as:

$$NNH = \frac{1}{Risk_{treatment} - Risk_{control}}$$

This metric indicates how many patients need to be treated for one additional adverse event to occur. In the same trial mentioned above, serious adverse events occurred in 15% of patients in the control group (B) and 20% of those receiving the intervention (A). This represents an absolute risk increase of 5 percentage points, corresponding to a NNH of 20 (i.e., $100/5 = 20$). In other words, for every 20 patients treated with A instead of B, one additional serious adverse event would be expected over the study period. When this harm is considered alongside a NNT of 10, the balance becomes clearer. For every 10 patients treated, one patient benefits, whereas for every 20 patients treated, one patient is harmed. Put differently, a patient is twice as likely to benefit as to experience harm. This framing helps convey the trade-off in practical terms; although the intervention carries an increased risk of adverse events, the probability of benefit outweighs the risk, albeit not overwhelmingly. The ratio between NNH and NNT is the likelihood to be helped or harmed (LHH).

The LHH integrates benefit and harm into a single metric:

$$LHH = \frac{NNH}{NNT}$$

An LHH greater than 1 indicates that benefit outweighs harm. For instance, an LHH of 2 suggests that patients are approximately 2 times more likely to benefit than to be harmed. This measure is particularly useful in clinical decision-making, as it provides a balanced perspective on treatment effects.

3.2. Annualized Number Needed to Treat (aNNT)

The annualized number needed to treat (aNNT) expresses how many patients need to be treated for one year to prevent one additional adverse event, taking into account the rate at which events occur over time [5]. Unlike the conventional NNT based on cumulative risks, the annualized NNT is derived from incidence rates, making it more appropriate when follow-up times vary or when time-to-event data are analyzed. In this approach, the key quantity is the incidence rate difference (IRD) between the control and treatment groups, calculated as the difference in events per person-year. The annualized NNT is then obtained as the reciprocal of this difference:

$$aNNT = \frac{1}{IRD}$$

This method assumes a relatively constant hazard over time and is particularly useful in studies reporting results as events per person-time rather than cumulative risks. For example, suppose a study reports an incidence rate of 4 events per 100 person-years in the control group and 2 events per 100 person-years in the treatment group. The incidence rate difference is 2 events per 100 person-years, or 0.02 per person-year. The annualized NNT is therefore $1/0.02 = 50$. This means that 50 patients need to be treated for one year to prevent one additional event.

4. Recommendations for Reporting RCT Results

To improve the interpretability and clinical relevance of RCTs, we propose the following methodological recommendations:

1. *Report both relative and absolute measures of effect.*
Relative measures alone are insufficient.
2. *Include NNT, aNNT, and NNH and corresponding 95% CI in all clinical trials.*
These metrics provide actionable insights.
3. *Clarify the distinction between hazard ratio and risk ratio in the data presentation.*
Avoid referring to them interchangeably.
4. *Enhance editorial oversight.*

Journals should ensure complete and transparent data reporting.

5. Conclusions

The evaluation of treatment effects in RCTs requires a nuanced and multidimensional approach. While relative measures such as hazard ratios and risk ratios are statistically informative, they are insufficient for comprehensive interpretation (Table 1). Absolute measures, including ARR, NNT, aNNT, and NNH, are indispensable for understanding the real-world impact of interventions and for guiding clinical decisions (Table 1). Furthermore, integrated metrics such as the likelihood to be helped or harmed provide valuable insights

into the balance between benefit and risk. Ultimately, improving the reporting and interpretation of effect measures is essential for bridging the gap between research and practice. By adopting a more transparent and patient-centered approach, the medical community can ensure that clinical decisions are grounded in a complete and accurate understanding of the evidence.

Table 1. Key measures of treatment effect: formulas, meaning, strengths, and limitations.

Measure	Formula	What It Represents	Strengths	Limitations
Risk Ratio (RR)	$\text{Risk}_{\text{treatment}} / \text{Risk}_{\text{control}}$	Relative probability of an event	Easy to understand; widely used	Ignores timing of events; may overemphasize effects
Hazard Ratio (HR)	$\text{Hazard rate}_{\text{treatment}} / \text{Hazard rate}_{\text{control}}$	Relative instantaneous risk over follow-up (estimated)	Accounts for time-to-event	Often misinterpreted as RR; less intuitive
Incidence Rate Ratio (IRR)	$\text{Incidence Rate}_{\text{treatment}} / \text{Incidence rate}_{\text{control}}$	Relative instantaneous risk over follow-up (observed)	Accounts for time-to-event	Often misinterpreted as RR; less intuitive
Absolute Risk Reduction (ARR)	$\text{Risk}_{\text{control}} - \text{Risk}_{\text{treatment}}$	Absolute difference in event probability	Direct measure of benefit	Depends on baseline risk
Number Needed to Treat (NNT)	$1 / \text{ARR}$	Patients needed to treat to prevent one event	Clinically intuitive; patient-centered	Varies with baseline risk; time-dependent
Number Needed to Harm (NNH)	$1 / \text{Risk}_{\text{treatment}} - \text{Risk}_{\text{control}}$	Patients treated for one additional adverse event	Clinically intuitive; patient-centered	Same limitations as NNT
Likelihood to be Helped or Harmed (LHH)	NNH / NNT	Balance between benefit and harm	Integrates benefit-risk	Oversimplifies complex outcomes
Annualized NNT (aNNT)	$1 / \text{IRD}$	Patients treated per year to prevent one event	Accounts for time and incidence rates	Assumes constant hazard

IRD = Incidence rate difference.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Campese, V.M. Truth and Pitfalls of Evidence-Based Medicine. *Kidney Dial.* **2025**, *5*, 38. [\[CrossRef\]](#)
2. Tripepi, G.; Jager, K.J.; Dekker, F.W.; Wanner, C.; Zoccali, C. Measures of effect: Relative risks, odds ratios, risk difference, and ‘number needed to treat’. *Kidney Int.* **2007**, *72*, 789–791. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Altman, D.G. Confidence intervals for the number needed to treat. *BMJ* **1998**, *317*, 1309–1312. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Brode, W.M. Number needed to treat. *N. Eng. J. Med.* **2026**, *394*, 1152–1153. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Mayne, T.J.; Whalen, E.; Vu, A. Annualized was found better than absolute risk reduction in the calculation of number needed to treat in chronic conditions. *J. Clin. Epidemiol.* **2006**, *59*, 217–223. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.