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VIEWPOINT

A Case for Using Relative Rather Than Absolute Noninferiority Margins in Clinical Trials

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Noninferiority trials are conducted to demonstrate that one therapy is not associated with an unacceptably high risk compared to another therapy. The maximum acceptable excess risk is defined in noninferiority trials by a "noninferiority margin," and if the difference in risk between the therapy of interest and the comparator therapy does not exceed the noninferiority margin, then the new therapy is considered safe, or "as good as" the comparator therapy.[1,2]

The noninferiority margin can be expressed as an absolute or relative risk difference.[3] Absolute rather than relative noninferiority margins are frequently used in cardiovascular trials. Unfortunately, absolute noninferiority margins are scientifically less robust than relative noninferiority margins and can lead to inaccurate conclusions regarding the safety of new therapies.[4] This paper will attempt to describe why the issues associated with absolute margins should preclude them from being used, after first attempting to debunk 2 common arguments used in favor of absolute vs relative noninferiority margins in clinical trials.

DEBUNKING OF 2 COMMON ARGUMENTS IN FAVOR OF ABSOLUTE NONINFERIORITY MARGINS

#1. Absolute risks are more interpretable: A common argument favoring the use of absolute noninferiority margins is that absolute risk differences are more clinically relevant and easier to interpret than relative risk differences.[1] The common practice in clinical trials to derive the absolute margin as the expected event rate multiplied by the maximally acceptable relative risk directly contradicts this argument.[5]

#2. Absolute noninferiority margins have better statistical power: A common reason for ultimately using absolute rather than relative margins in noninferiority trials is the fact that for any given true event rate (ie, the population event rate or the event rate that would be observed if we enrolled an infinite number of patients from the intended study population), a trial that uses an absolute noninferiority margin will have better statistical power to show noninferiority than a trial that uses a relative noninferiority margin corresponding to the same difference.[5] For example, if the true event rate in both the treatment arm and the control arm is 7.5% and patients are randomized 1:1 to treatment vs control, then a trial with an absolute margin of 3% will require 3,300 patients to achieve 90% power, whereas a trial with a relative margin of 1.4 will require 4,640 patients to achieve 90% power.

This apparent benefit of an absolute noninferiority margin is, however, an illusion related to the fact that if we were to conduct a large number of trials in which both treatment and control groups are sampled independently from populations with 7.5% event rates, then the relative difference would exceed 1.4 more often than the absolute difference would exceed 3%. Consider, for example, a trial in which the observed event rates are 6% in the control arm and 9% in the treatment arm. In this trial, the absolute difference is 3% and the relative risk is 1.5, but the observed risk difference corresponds to a 50% increased risk irrespectively. Rather than reverting to using an absolute noninferiority margin because the

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TABLE 1 Consequences of Lower and Higher Than Anticipated Event Rates in Superiority and Noninferiority Trials

	Superiority Trial[a]	Noninferiority Trial Relative Margin	Noninferiority Trial Absolute Margin
Lower than anticipated event rates			
Certainty of estimated treatment differences	Less certain	Less certain	Less certain
Likelihood of a positive/successful trial	Less likely	Less likely	More likely
Higher than anticipated event rates			
Certainty of estimated treatment differences	More certain	More certain	More certain
Likelihood of a positive/successful trial	More likely	More likely	Less likely

Statistical power increases rather than decreases if event rates are lower than anticipated and decreases rather than increases if event rates are higher than anticipated in noninferiority trials that use absolute noninferiority margins. As a consequence, these trials are more likely to meet the criteria for noninferiority in the presence of lower than anticipated event rates, despite there being greater uncertainty regarding the true treatment difference. In this regard, noninferiority trials using absolute noninferiority margins directly contrast with superiority trials and noninferiority trials with relative noninferiority margins, in which both the certainty of the treatment effects and the likelihood of a 'positive' trial increase with increasing event rates. [a]Under the assumption that the treatment being studied in the superiority trial is truly superior to the control treatment.

estimated sample size would be lower than if a corresponding relative margin was used, a more permissive relative margin should be allowed.

LOWER THAN ANTICIPATED EVENT RATES IN A CLINICAL TRIAL RESULT IN LESS ROBUST ESTIMATES OF TREATMENT EFFECTS AND REDUCE THE CHANCE OF A 'POSITIVE' RESULT IN SUPERIORITY TRIALS AND NONINFERIORITY TRIALS WITH RELATIVE MARGINS, BUT INCREASE THE CHANCE OF A 'POSITIVE' RESULT IN NONINFERIORITY TRIALS WITH ABSOLUTE MARGINS

Because an absolute noninferiority margin is fixed irrespective of what the observed event rates in the trial are, it corresponds to a relatively larger difference when event rates are low and is therefore easier to 'meet' when event rates are low. In other words, the statistical power of a noninferiority trial with an absolute noninferiority margin is greater the lower the observed event rates. This is counterintuitive since the certainty of the effect estimate is proportional to the event rate (ie, increases with increasing event rates) and contrasts sharply with the traditional superiority trial designed to demonstrate that one therapy is better than another (Table 1).[1]

In superiority trials and noninferiority trials with relative noninferiority margins, a higher event rate leads to a more precise estimate of the treatment effect and increases power to meet the trial's primary endpoint. Put differently, the more precisely the treatment difference can be estimated, the greater the likelihood of a 'positive' trial. In these types of trials, overestimation of event rates at the design stage will result in an overestimation of statistical power and is therefore undesirable.

Conversely, a noninferiority trial using an absolute margin will be more likely to be 'positive' if the event rate is lower, despite the fact that the treatment effect will be less precisely estimated with lower event rates. This introduces an incentive for the trialists to overestimate the event rate in such trials.

We recently demonstrated the impact of this issue on the existing evidence base using coronary stent trials as an example.[5] Out of 58 trials, 55 (94.8%) used absolute margins, and 77% of the trials overestimated their event rates. Moreover, more than one-third of the trials that met noninferiority would not have done so if relative margins corresponding to the relative risk difference that was used as the basis for the absolute noninferiority at the design stage had been used.[5]

To the author, the most significant problem with absolute noninferiority margins is that they incentivize trialists to design trials that, because they use event rate assumptions that are too high, are underpowered to provide robust estimates of the treatment effect but overpowered to demonstrate noninferiority with too permissive criteria for noninferiority.[5] The root of this problem is the decoupling of the relationship between better precision in estimated treatment effects and the likelihood of a 'positive' trial in noninferiority trials using absolute noninferiority margins.

CONCLUSIONS

In summary, whereas both absolute and relative risks are important to patients, relative noninferiority margins are scientifically more robust than absolute noninferiority margins and should be used.

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REFERENCES

1. Pocock SJ, Clayton TC, Stone GW. Challenging issues in clinical trial design: part 4 of a 4-part series on statistics for clinical trials. *J Am Coll Cardiol*. 2015;66(25):2886–2898. https://doi.org/10.1016/j.jacc.2015.10.051

2. Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med*. 2017;377(14):1357–1367. https://doi.org/10.1056/NEJMra1510063

3. Le Henanff A, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. *JAMA*. 2006;295(10):1147–1151. https://doi.org/10.1001/jama.295.10.1147

4. Kaul S, Diamond GA, Weintraub WS. Trials and tribulations of non-inferiority: the ximelagatran experience. *J Am Coll Cardiol*. 2005;46(11):1986–1995. https://doi.org/10.1016/j.jacc.2005.07.062

5. Simonato M, Ben-Yehuda O, Vincent F, Zhang Z, Redfors B. Consequences of inaccurate assumptions in coronary stent noninferiority trials: a systematic review and meta-analysis. *JAMA Cardiol*. 2022;7(3):320–327. https://doi.org/10.1001/jamacardio.2021.5724

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