

ENDGAMES

STATISTICAL QUESTION

Randomised controlled trials: evaluating and communicating treatment effects

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Researchers investigated the efficacy of the anticoagulant fondaparinux in older acute medical inpatients at moderate to high risk of venous thromboembolism. A double blind randomised placebo controlled trial study design was used. The intervention was 2.5 mg fondaparinux subcutaneously once a day for six to 14 days. Participants were 849 acute medical patients aged 60 years or more who were admitted to hospital.¹ The primary outcome was venous thromboembolism detected by routine bilateral venography. In total, 644 patients (75.9%) were available for the analysis of the primary outcome. Venous thromboembolism was detected in 5.6% (18/321) of patients treated with fondaparinux and 10.4% (34/323) of those given placebo. The reduction in risk of venous thromboembolism with fondaparinux compared with placebo represented an absolute risk reduction of 4.9% (95% confidence interval 0.7% to 9.2%) and relative risk reduction of 46.7% (7.7% to 69.3%). The number needed to treat was 20.4.

Which of the following statements, if any, are true?

- The absolute risk reduction of venous thromboembolism for fondaparinux compared with placebo was significant
- The relative risk reduction of 46.7% of venous thromboembolism with fondaparinux compared with placebo represented a relative risk of 0.533
- The number needed to treat estimates that, on average, for every 20.4 patients given fondaparinux one would not develop venous thromboembolism

Answers

Statements *a* and *b* are true, whereas *c* is false.

The aim of the trial was to investigate the efficacy of the anticoagulant fondaparinux in older acute medical inpatients at moderate to high risk of venous thromboembolism. The intervention (fondaparinux) reduced the proportion of patients with venous thromboembolism compared with placebo (5.6% v 10.5%). The effects of the intervention when compared with

placebo were reported using absolute risk reduction, relative risk reduction, and number needed to treat.

The absolute risk reduction was the difference between the intervention and the control in the risk of venous thromboembolism. It is the risk for placebo minus that for the intervention. The absolute risk reduction is sometimes called the risk difference. It may be expressed as a probability or percentage, and it describes by how much the intervention reduces the risk of the primary endpoint compared with the control. In the example above, the absolute risk reduction was $10.5\% - 5.6\% = 4.9\%$ (95% confidence interval 0.7% to 9.2%). Because the 95% confidence interval for the absolute risk reduction did not include zero, and both limits were above zero, the reduction in risk for the intervention was significant when compared with the placebo (*a* is true). A previous question described how conclusions about significance can be made on the basis of the 95% confidence interval.²

The relative risk reduction is an alternative way of expressing the absolute risk reduction. It is derived by dividing the absolute risk reduction in the primary endpoint for the intervention compared with placebo by the risk of the primary endpoint for the placebo group. It represents by how much the intervention reduced the risk of venous thromboembolism relative to the placebo. For the trial above, the relative risk reduction equals $4.9\% \div 10.5\% = 0.467$ or 46.7%.

Relative risk is directly related to the relative risk reduction. The relative risk compares the risk of venous thromboembolism between treatment groups. It is derived as the ratio of the risk (probability) of venous thromboembolism if treated with fondaparinux to the risk if treated with placebo. For the example above, the relative risk was $5.6\% \div 10.5\% = 0.533$. Therefore, the risk to patients treated with fondaparinux was 0.533 times that of those treated with placebo—that is, the risk was reduced by 46.7% compared with those treated with placebo (*b* is true). This represents a relative risk reduction of 0.467 as described above. Relative risks have been described in a previous question.³

The number needed to treat is sometimes called the number needed to treat to benefit. It is derived by calculating the reciprocal of the absolute risk reduction, with the absolute risk reduction expressed as a proportion. For the trial above, the number needed to treat was $1 \div 0.049 = 20.4$. This measure of treatment effect describes how many patients would need to be treated with the intervention for one fewer patient to experience venous thromboembolism, compared with if they had been treated with placebo (*c* is false). On average, if 20.4 patients were treated with fondaparinux, 1.14 participants (5.6%) would be expected to have a venous thromboembolism, whereas if those same patients were treated with placebo then 2.14 (10.5%) would develop venous thromboembolism. To have direct clinical relevance, the number needed to treat would be rounded to 22 patients.

Statement *c*—that, on average, for every 20.4 patients treated with fondaparinux, one would not develop venous thromboembolism—is a common misinterpretation of the number needed to treat (*c* is false). The statement indicates that, on average, for every 20.4 patients treated with fondaparinux, one would not develop venous thromboembolism, whereas the remaining 19.4 would. Number needed to treat does not indicate how many patients need to be treated with the intervention for one patient to benefit. It is a measure of the therapeutic benefit of fondaparinux compared with placebo, as described.

The above trial looked at the reduction in the risk of a bad outcome (venous thromboembolism) with the intervention versus placebo. Therefore, absolute risk reduction and relative risk reduction were apt descriptors of treatment benefit. However, if the aim of the trial had been to increase the probability of a good outcome, these descriptors may have been confusing. For example, a trial might investigate the effectiveness of a smoking cessation aid compared with placebo. The primary outcome might be abstinence at the end of treatment, and the intervention would be expected to benefit more participants compared with

placebo. In such circumstances, the terms “absolute benefit increase” and “relative benefit increase” have been suggested instead. These will be described in a later question.

When discussing the use of fondaparinux with a patient (or another healthcare professional), a clinician may wish to explain the potential benefits and risks of treatment without using specialist language. In this instance, the intended benefit is the prevention of a blood clot in the vein or lung, whereas the potential risks are a bleed. The use of similarly clear language to convey statistical information while avoiding certain measures of treatment effect is also recommended. Rather than quoting the relative risk reduction using percentages to describe the benefits of the intervention, it would be more helpful to use the absolute risk reduction, describe with natural frequencies, and to personalise the message. For example, a clinician could explain that “Out of 100 patients like you, about 11 would be expected to develop a blood clot if they were not given a preventive drug, compared with an expected six patients out of 100 who were given the drug fondaparinux.” The use of relative risk reduction can be misleading. For example, the statement that: “the rate of venous thromboembolism is almost halved in patients taking the drug,” although not incorrect, can appear to overstate the efficacy of the new drug.

Competing interests: None declared.

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