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ENDGAMES

STATISTICAL QUESTION

Interpreting hazard ratios

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The impact of isoniazid prophylaxis on mortality and tuberculosis in children with HIV was investigated using a double blind placebo controlled trial. The intervention was isoniazid given with co-trimoxazole either daily or three times a week. Control treatment was placebo isoniazid given with co-trimoxazole. The setting was two tertiary healthcare centres in South Africa. Participants were children with HIV aged 8 weeks and older. In total, 277 children were recruited and randomised to the intervention (n=139) or control treatment (n=138).[1]

The primary outcomes included the length of time after randomisation until death from any cause and the length of time after randomisation until the occurrence of tuberculosis. The initial results of the trial were reported after participants had been followed for a maximum of 500 days (median 5.7 months) During follow-up, mortality was significantly lower in the isoniazid group than in the placebo group (8% (n=11) *v* 16% (n=21); hazard ratio 0.46, 95% confidence interval 0.22 to 0.95). Furthermore, the risk of tuberculosis was also significantly reduced in the isoniazid group (4% (n=5) *v* 10% (n=13); 0.28, 0.10 to 0.78). The researchers concluded that for children with HIV, isoniazid prophylaxis has an early survival benefit and reduces the risk of tuberculosis.

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

a) When calculating the hazard ratio of death, it was assumed that the death rate was constant during follow-up for each treatment group

b) The intervention group had a 54% lower risk of mortality than the control group at any time during follow-up

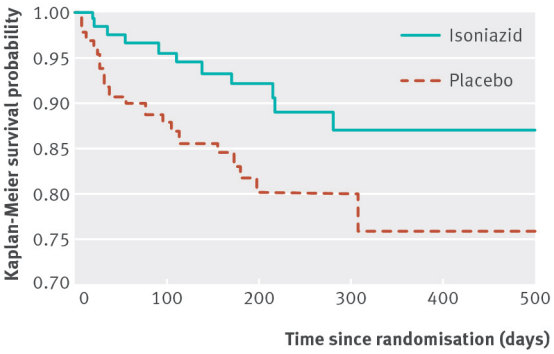
c) The hazard ratio of death is the ratio of the number of deaths in the intervention group to the number in the control group at follow-up

d) The hazard ratio of death provides an estimate of the length of survival

Answers

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

The aim of the trial was to establish the impact of isoniazid prophylaxis on mortality and tuberculosis in children with HIV. The outcome measures included the length of time after randomisation until death from any causes. These times are referred to as "time to event" or "survival" data, described in a previous question.[2] The methodology used to analyse such data is known as Kaplan-Meier survival analysis, which was originally developed to analyse data where the endpoint was death, so the times were referred to as "survival data." In the above trial, if death occurred during follow-up the survival time was termed "exact" and if the child was still alive at the end of follow-up the survival time was "censored." All of the survival times, whether exact or censored, were used to compare treatment groups in the length of time after randomisation until death. The survival times for the treatment groups were displayed using a Kaplan-Meier survival plot (figure), the interpretation of which has been described in a previous question.[3]



Kaplan-Meier plot of survival time for the intervention (isoniazid given with co-trimoxazole) compared with control treatment (placebo isoniazid given with co-trimoxazole)

The hazard ratio, sometimes called a relative hazard, is typically used to compare time to event data between two treatment groups. The hazard ratio of death for the intervention group compared with the control group was 0.46 (0.22 to 0.95). The hazard ratio was derived as the ratio of the hazard of death for

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the intervention group to the hazard of death for the placebo group across the study period. To derive the hazard of death for a treatment group, the study period was conceptually divided into very short time intervals. The hazard of death was derived for each time interval and was equal to the probability of death in the interval divided by the length of the interval. Therefore, for each time interval the hazard of death represented the death rate or risk of death in the interval. When deriving the hazard ratio, the hazard rate (death rate) for either treatment group may not be constant throughout follow-up (*a* is false). However, it is assumed that the ratio of the death rates is constant across the study period and is the same, if only approximately, for each time interval. Hence the hazard ratio represents the risk of death in the isoniazid prophylaxis group compared with the placebo group at any time during the study period.

The hazard ratio of death for the intervention group compared with the control group was 0.46 (0.22 to 0.95), which is smaller than unity (1.0). Therefore, the hazard of death in the isoniazid prophylaxis group was less than that in the control group. At any time during follow-up the intervention group was 0.46 times as likely to die, representing a 54% reduction in risk, compared with the control group (*b* is true). Because the 95% confidence interval for the hazard ratio did not include unity, as described in a previous question,[4] the hazard ratio was significantly different from unity. In particular, the limits for the associated 95% confidence interval were smaller than unity and therefore the risk of death was significantly lower in the isoniazid prophylaxis group than in the control group.

The hazard ratio compared the risk of death between the two treatment groups throughout the study period. It does not provide any indication of the numbers of deaths between the treatment groups at follow-up (*c* is false). Neither does the hazard ratio give any indication of the length of time that children would have survived after randomisation to treatment groups (*d* is false). For that reason it may be useful to provide some indication of the overall survival. At the end of follow-up (500 days), the cumulative probability of survival was about 0.76 for the isoniazid prophylaxis group and about 0.87 for the placebo group, reflecting the reduced mortality in the intervention group as indicated by the hazard ratio. Median survival time is a useful indicator of average survival and is the time during follow-up at which there is a probability of 0.5 of survival beyond.[5] However, it was not possible to estimate the median survival time for the treatment groups in the above trial because the cumulative probability of survival did not reach 0.5 or lower (figure).

An understanding of hazard ratios helps clinicians interpret research findings reported in the scientific literature and may inform decisions about what treatments can be recommended to patients. It is clear, however, that statistical concepts such as hazard ratios are unlikely to be meaningful to patients. For patients to make a fully informed decision, clinicians need to explain the risks and benefits of treatment clearly and comprehensively and not cloud their explanation with overly complex statistical terminology. Hazard ratios in isolation provide no indication of the relative numbers of deaths between treatment groups after follow-up or the potential length of survival. Therefore, some additional information about overall survival needs to be considered. This may include the cumulative survival probabilities at the end of follow-up or the median survival times if available. As described in previous questions,[2 5] the use of probabilities may not be helpful, and natural frequencies should be considered instead when describing the merits of treatment.

Competing interests: None declared.

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