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Sir,
Response to Hernández-Martínez *et al*

This article has been corrected since Advance Online Publication and a corrigendum is also printed in this issue

The letter 'Local safety of repeated intravitreal Ozurdex' by Hernández-Martinez *et al*[1] highlights the impact of intravitreal Dexamethason-implant (Ozurdex) on lens opacification. They showed in a retrospective review that four out of five (BRVO) or six (CRVO) eyes receiving a second Ozurdex showed a progression of cataract requiring surgery. As the Geneva study has shown,[2] Ozurdex is an effective treatment option for macular edema due to RVO. While our study[3] confirms these data, it furthermore shows a significant progression in cataract formation after the third intravitreal injection. Therefore, it is mandatory to consider along with age and intraocular pressure the lens status when using intravitreal Ozurdex. In the mentioned retrospective case series by Hernández-Martinez *et al*, it is not clear whether there is a progression of an existing cataract to a cataract requiring surgery or clear lenses showing a beginning of cataract formation. Furthermore, no objective classification of lens opacification was assessed to show which kind of lens opacification shows a significant progression requiring surgery. It is also necessary to investigate recurrence rates, treatment intervals and the data should be supplemented by a clear follow-up time. We agree that long-term follow-up data are needed to confirm present observations. As the adequate treatment of macular edema due to RVO is still a challenge, treatment possibilities including intravitreal steroids, anti-VEGF substances, laser photocoagulation or combinations are safe and effective options after taking into account the pathogenesis of retinal vein occlusion.

Conflict of interest

The author declares no conflict of interest.

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Sir,
Interval censoring and competing risks when reporting results of glaucoma surgery

Dr Dulku[1] criticised the Kaplan–Meier analysis that Drs Anand and Wechsler[2] used to assess failure and complications after deep sclerectomy with mitomycin C in eyes with failed glaucoma surgery, pseudophakia, or both. He pointed out that these events had occurred at unknown times before the visit at which they were recorded, making the survival curves too good, and recommended that interval censoring[3] adjust for this bias. However, competing risk bias should additionally be considered.

Drs Anand and Wechsler operated on 82 patients,[2] who were on average 76 years old. A total of 20 patients died during the over 5-year-long observation period.[2] The authors do not mention how they dealt statistically with patients who died.[2] We dare expect they were censored just like the patients who became too ill to attend their clinic.[2] However, a fundamental difference exists between these two groups: only the latter group of patients remained at risk after censoring.

After censoring, the Kaplan–Meier curve will drop proportionately more with any subsequent event as compared with what it would have dropped had censoring not taken place. A key assumption is that censoring is independent of the risk of experiencing the event of interest, that is, the risk is equal before and after censoring.[4] Clearly, this assumption is not met if any subjects die: the survival curve will become too pessimistic. Death is a competing risk event, which should be dealt with methods other than censoring,[5,6] such as cumulative incidence analysis,[7] found both in the

R package mentioned and in a number of commercial packages.

The paper of Drs Zhang and Sun,[3] which Dr Dulku[1] cites, briefly discusses interval censoring in face of competing risks. However, commercial software for this purpose is not yet marketed. Formal adjustment is available either for interval censoring[1,3,6] or for competing risks.[5,7–10] To address simultaneously both biases, one reasonable approach at present is to undertake cumulative incidence analysis and to plot two curves, the first modelling the event of interest as occurring when it was recorded, and the second assigning it to the immediately preceding visit. The former curve will exaggerate the probability of success and the latter the probability of failure. Alternatively, a cumulative incidence curve based on the midpoint of the review interval may be used as an approximation of interval censoring.[9]

Interval censoring and competing risks bias in survival analysis are ill known to authors, reviewers, and readers, risking misinterpretation of study results.

Conflict of interest

The authors declare no conflict of interest.

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Sir,
Reply to Kivelä *et al*

Kivelä *et al*[1] raise an important point regarding survival analysis in glaucoma surgery in that bias is caused when the competing risk of death is not taken into account. A glaucoma operation that does not fail in the patient's lifetime can be considered a complete success (as long as the patient does not die before they could be expected to benefit from the procedure). The current implementation of survival analysis in glaucoma surgery does not account for this by considering such patients still at risk of failure even after they have died.

Kivelä *et al*[1] note that current statistical packages do not yet allow for the routine analysis of competing risks data subject to interval censoring. While methods have been devised to deal with such data,[2,3] such techniques are considerably more difficult to apply than standard Kaplan–Meier survival analysis.

As the proportion of deaths in the population decreases, the effect of the competing risk of death will reduce. Studies with shorter follow-up are less likely to encounter bias than those with longer follow-up. However, death is a common outcome in studies with longer follow-up. The 20-year outcomes of trabeculectomy have been reported[4] and in this study, 21% of patients were censored due to death. In the TVT study,[5] 13% of patients had died by 5 years. Surgical failure is, therefore, likely to have been overestimated in these studies.

Competing risks analysis in glaucoma studies could be extended to competing risks other than death. For trabeculectomy, an important competing risk is the requirement for needling. Current studies usually ignore needling as an event;[5] competing risks analysis would provide a mechanism whereby this could be taken into account.

Given the above, it may be necessary to rethink the application of survival analysis to glaucoma surgery so that we can make more accurate predictions of survival and better use of the available data. A more sophisticated approach will ultimately allow us to more accurately describe the likely postoperative course when counseling patients regarding glaucoma surgery.

Conflict of interest

The author declares no conflict of interest.

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1 Kivelä T, Kujala E, Forsman E, Vesti E. Interval censoring and competing risks when reporting results of glaucoma surgery. *Eye* 2014; **28**(3): 362–363.