

## Is There Such Thing as an Optimum Number of Intravitreal Injections Before Incurring an Increased Risk of ENDOPHTHALMITIS?

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### Purpose

Intravitreal injections [IVIs] are administered in ever increasing numbers, nowadays well into many tens or even hundreds. Leading drivers are : the ongoing nature of modern therapy regimens, the widespread availability of IVIs in health systems worldwide and the hesitancy of the treating physicians to discontinue treatment. This gives rise to a **culture of: "One cannot stop injecting"**. While most studies are focused on a single injection risk of endophthalmitis, we also assessed the risk of multiple injections per patient. To avoid selection bias, we demanded the prospective declaration of all suspected endophthalmitis (antibiotics vials dispensed were numbered and needed to be accounted for).

### Aim

1. To determine the threshold number of injections above which there might be an increased risk of endophthalmitis in a prospective data collection over a 10 year-period
2. To analyse if the frequency of injections prior to endophthalmitis had an influence on its risk profile

### Methods

Baseline statistics were analysed using STATA 18 software. Univariate linear logistic regression was used to calculate the increased risk of endophthalmitis related to the number of injections performed in each eye as well as corrected for the time delay since the first injection. Patients were stratified according to the total number of injections performed in each eye with a cut-off value of under 60 or over or equal to 60 injections with 95% confidence intervals. Multivariate analysis was performed with adjustment towards time elapsed from the first injection and type of drug administered to assess the Odds Ratio of increased risk per each injection. (Wald test). The risk of endophthalmitis was also analysed according to the laterality of the eye injected and the sex of the patients. Truncated negative binomial regression compared the mean number of injections performed during the LAST year prior to endophthalmitis to the mean number of injections performed during the LAST year in the non-endophthalmitis group.

### Results

Our prospective study found an incidence of 26 endophthalmitis per 64 743 injections (rate of 0.04% or 1 in 2490 injections) over a ten-year period (2014 to 2023). The total number of patients was 3 840 (0.67% 1/147). This represents 13 629 patient-years of follow-up (mean follow-up of each individual patient was 3.5 years). The yearly anti-VEGF number of injections from 2014 to 2023 remained stable with a mean number of 7 119 ± 369 injections per year. Mean number of IVI's in the non-endophthalmitis (group 1): 18.4 ± 17.9 injections vs. a mean number of 36.5 ± 25.5 injections for patients in the endophthalmitis (group 2). The endophthalmitis rate was 0.03% in group 1 (19/62 364 or 1 in 3 282) vs. 0.29 % in group 2 (7/2 405 or 1 in 344). Stratification of the total number of injection performed demonstrated that the proportion of eyes presenting with presumed endophthalmitis after IVI increased drastically when the number of injections per eye exceeded 60 injections, i.e.10 times! This can be visualized as the cumulative hazard soars dramatically around 60 -70 IVI's [Fig. 1; Fig. 2]. Univariate linear logistic regression (Wald test = 25.6; p = 0.0000) shows an increased risk with an Odds ratio (OR) of 1.0358 per each injection performed.

**Subgroup analysis showed a significant doubling of the endophthalmitis risk after 20 IVIs, trebling after 30 IVIs and quintupling after 45 IVIs. [Fig. 3]**

The mean number of injections during the LAST year prior to endophthalmitis was 8.33 ± 3.33 while it was only 3.69 ± 2,37 in the non-endophthalmitis group.

**Patients who eventually got endophthalmitis had 148% MORE injections during the year prior to endophthalmitis. [Fig. 4]**

### Conclusion

An earlier analysis of injections performed between 2004 to 2011 showed an incidence of 0.0075% per injection (95% confidence interval: 0.0026 – 0.0220%) or 1 case per 13 337 IVIs. Data collection was retrospective only [Casparis et al. 2014].

Our prospective study (0.04%) managed to replicate the internationally published endophthalmitis rate of between 0.035% - 0.05%, so it is not an outlier.

The outstanding difference between today's IVI-population and that of 20 years ago is that a much higher proportion of today's patients have already undergone a very high number of IVI's, many above 60 and some well into three-digit numbers.

**A ten-fold increased risk of endophthalmitis above 60 injections ought to re-balance the risk/benefit analysis requiring individual justification in each individual case and for each additional injection.**

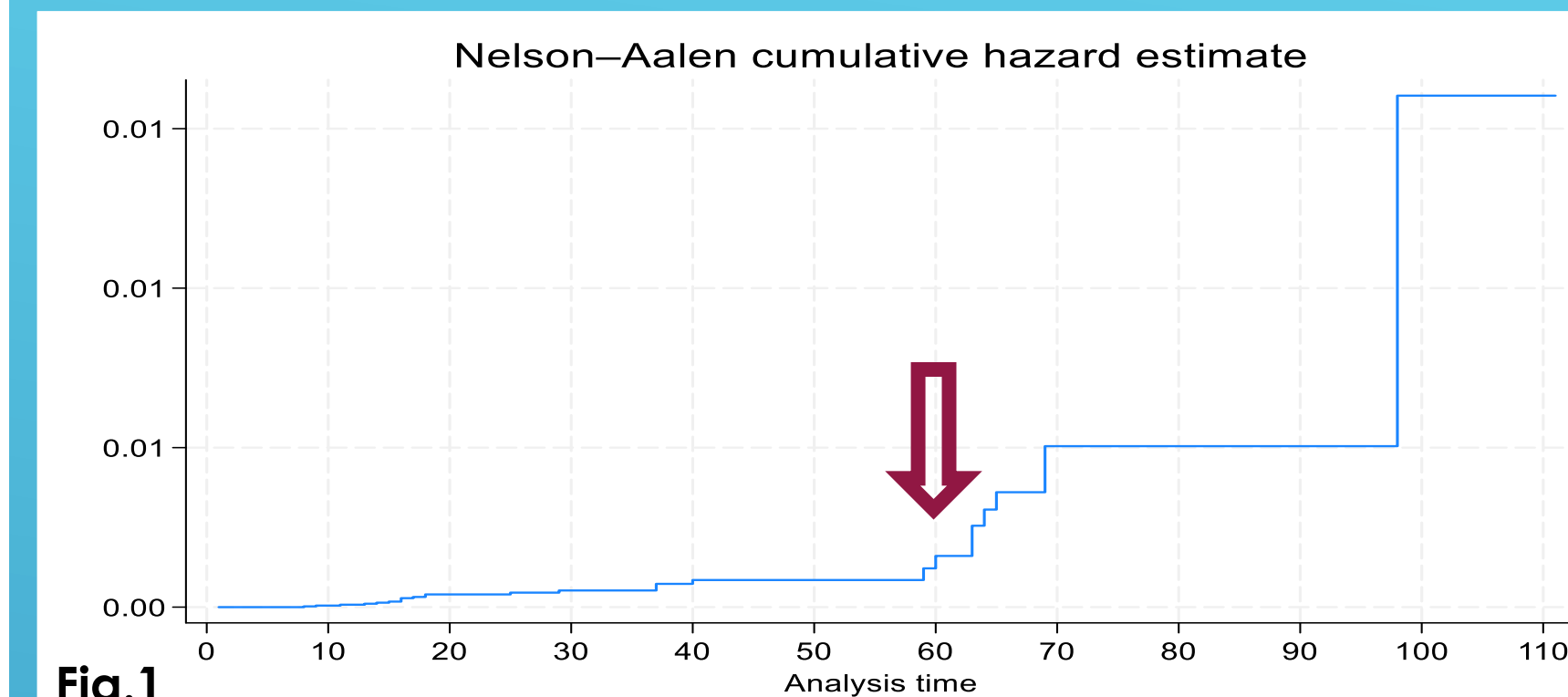


Fig. 1

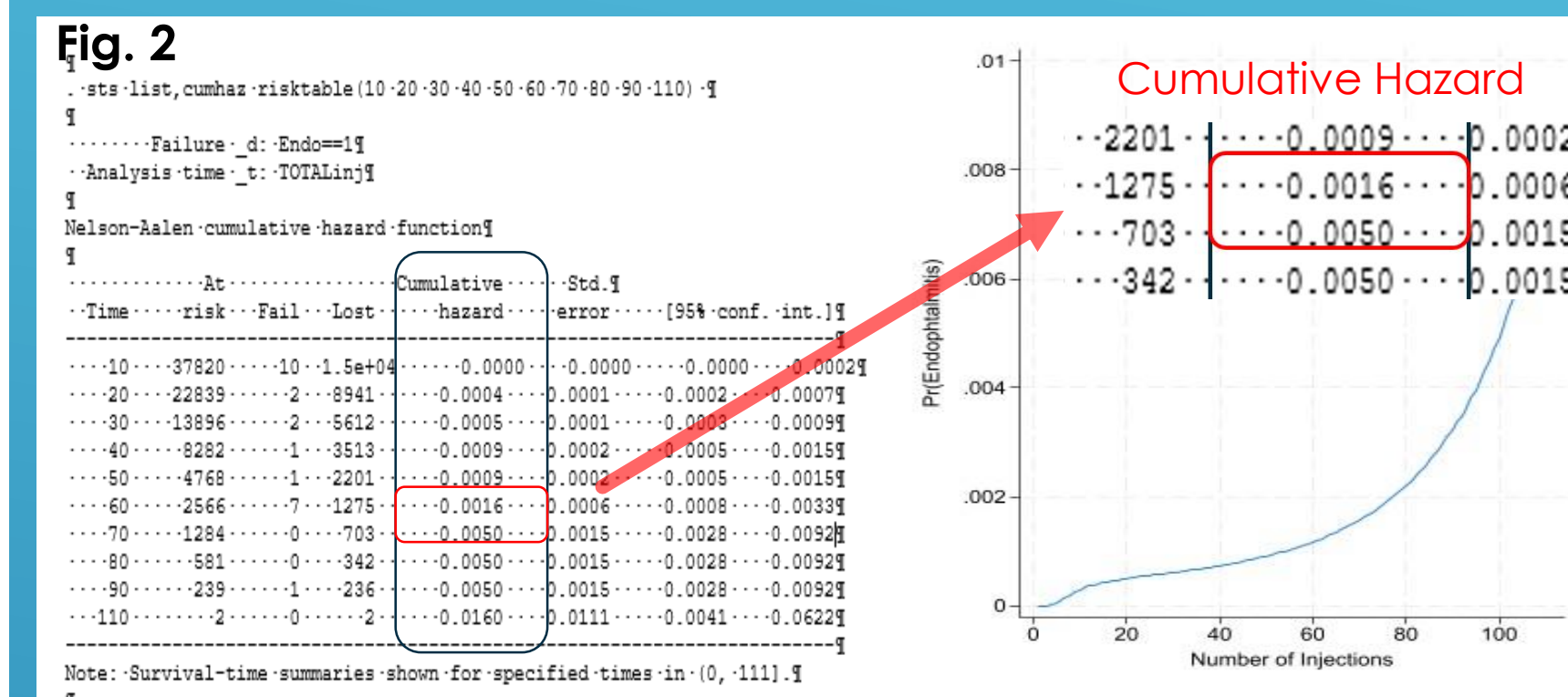


Fig. 2

**Endophthalmitis Risk:**  
➤ >60 injections shows an OR of 9.6 (Wald test = 24.71; prob > chi² 0.0000).

- Subgroup analysis:**
- more than 20 injections: OR: 2.31 p=0.0341
  - more than 30 injections: OR: 3.35 p=0.0023
  - more than 45 injections: OR: 5.17 p=0.0001

Fig. 3

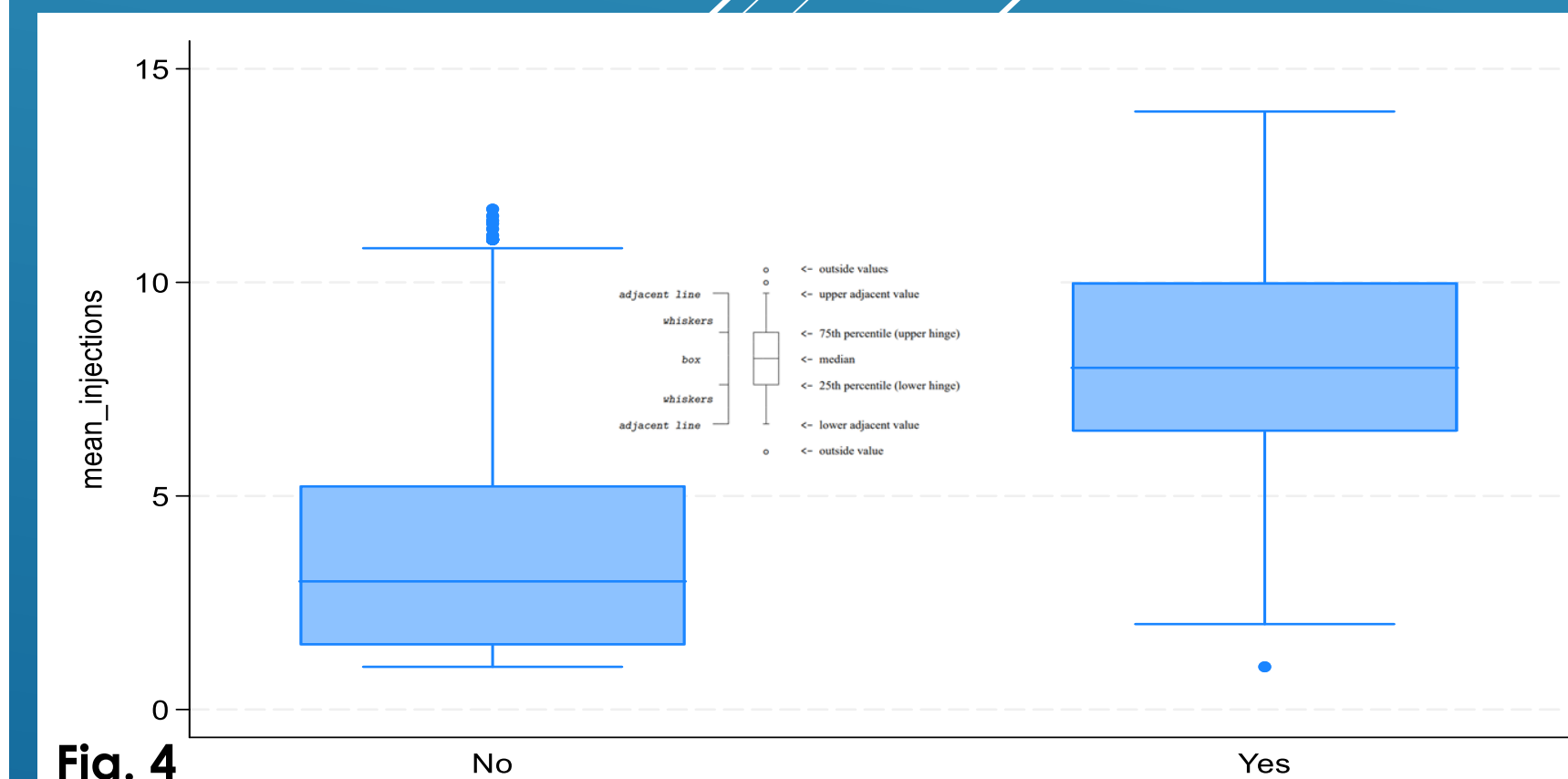


Fig. 4