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Frequency of intravitreal anti-vascular endothelial growth factor injections and risk of death: a systematic review with meta-analysis

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Abstract

Topic: To investigate whether an increasing number of intravitreal anti-vascular endothelial growth factor (VEGF) injections is associated with a higher mortality risk.

Clinical relevance: The issue of systemic safety of intravitreal anti-VEGF therapy has been long discussed. Evidence from meta-analyses of randomized studies has shown no increased risk of mortality in overall population, while some warning signal of higher mortality were found in diabetic patients exposed to intense and prolonged treatment. Concerns have been raised as to whether an increasing number of anti-VEGF injections could be associated with a higher mortality.

Methods: Randomized clinical trials enrolling arms with different intensity of anti-VEGF therapy were searched. The incidence rate ratio (IRR) of death with 95% confidence interval (CI) for receiving 5 injections was the primary outcome measure. The relationship between the number of injections and all-cause mortality was investigated. Separate regression analyses were conducted to investigate this relationship in subgroups of studies with different diseases and drugs.

Results: Fifty-two trials were included. An overall mortality rate of 1.02% and 3.36% was recorded at 12 and 24 months, respectively. Univariate regression showed that a larger number of injections was not associated with a significant increase in mortality both at 12 months (IRR=1.16, 95%CI=0.87-1.53; p=0.31) and at 24 months (IRR=1.05, 95%CI=0.95-1.15; p=0.34). According to subgroup analyses, a higher risk was marginally associated with an increasing number of injections in diabetic macular edema (DME) studies at 24 months (IRR=1.17, 95%CI=1.02-1.33; p=0.03).

Conclusion: No significant influence of anti-VEGF treatment intensity on mortality was shown, supporting a message of reassurance over safety concerns of this therapy. Marginal evidence of a higher risk associated with a more intense treatment was found in DME patients.
Introduction

Medical retina practice has completely changed following the introduction of intravitreal therapy with anti-vascular endothelial growth factor (anti-VEGF) agents, which could be considered as the most remarkable breakthrough in ophthalmology of the new century. This sight-saving therapy is the gold standard treatment for most common macular diseases, such as wet age related macular degeneration (AMD), diabetic macular edema (DME) and macular edema secondary to retinal vein occlusion (RVO). If the efficacy of these agents is a matter of fact, the safety has been a matter of discussion.

The risk of increased mortality associated with intravitreal anti-VEGF treatment has long been debated. On the one hand, randomized clinical trials (RCTs) have not shown any significant difference in mortality rates between patients treated with intravitreal anti-VEGFs and controls. On the other hand, some real-world retrospective studies have reported an increased mortality in patients receiving intravitreal anti-VEGF therapy, in particular when other cardiovascular risk factors were present. Meta-analysis studies showed no increased risk for death in the overall population treated with intravitreal anti-VEGFs, but concerns of higher mortality have been raised in diabetic patients receiving intensive intravitreal anti-VEGF therapy.

Recently, we sought to explore this issue through a meta-analysis of RCTs, giving a warning signal of higher mortality associated with an increasing number of anti-VEGF injections. This finding of a linear increase in mortality risk for increasing injections was somehow limited by the nature of that study, which primarily aimed at comparing mortality rates between those receiving anti-VEGFs and non-treated controls. However, given the noticeable clinical relevance of a theoretical mortality risk associated with injection number, we decided to further investigate this issue. For this reason, we conducted a systematic review with meta-analysis of RCTs enrolling arms with different intensity of intravitreal anti-VEGF therapy, with the purpose of
assessing whether there could be an association between mortality rate and number of anti-VEGF injections.

**Methods**

**Search methods and eligibility criteria**

This systematic review was conducted in accordance with the statements of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)\textsuperscript{13} and with the guidelines contained in the Cochrane Handbook \textsuperscript{14} (PRIMA checklist available as eTable 1 in Supplement). Pubmed and Embase databases, ClinicalTrials.gov website and the Cochrane Library were systematically searched from their inception to June 30\textsuperscript{th}, 2020. The search strategy is shown in eTable 2, available in Supplement. Reference lists of included articles were reviewed as well. The search was restricted to studies published in English and in peer reviewed journals, with no limitations about publication status and date. Institutional review board approval was waived because this study was a systematic review of published studies.

To be eligible, studies had to satisfy the following inclusion criteria: a) to feature a randomized design; b) to enroll patients receiving intravitreal anti-VEGF therapy with bevacizumab, ranibizumab or aflibercept for AMD, DME or macular edema secondary to RVO; c) to have a 1- to 3-year follow-up; d) to compare intravitreal anti-VEGF therapy versus a control group or to compare different anti-VEGF treatment regimens with the same agent; and d) to report all-cause mortality rate and information on injection number for each study arm. The possibility of having the two eyes of one subject randomized to different arms within the same trial was considered as an exclusion criterion. A design different from RCT, a diagnosis different from the ones reported above such as myopic choroidal neovascularization, polypoidal choroidal vasculopathy and proliferative diabetic
retinopathy, a follow-up shorter than 1 year or longer than 3 years, were also considered as exclusion criteria.

The primary outcome of interest was the relationship between the average number of injections in different study arms and the all-cause mortality rate. Separate regression analyses were conducted to investigate this relationship in subgroups of studies including patients with different diseases or using different drugs.

Data collection and Quality assessment

Data extraction was carried out by two independent investigators (M.F. and P.M.). In cases of disagreement, a third investigator (M.R.) was consulted to reach consensus. All-cause mortality rate was extracted from each arm of included RCTs, along with the number of patients and demographic characteristics (i.e. age and gender), the type and dosage of anti-VEGF agent, the number of injections, follow-up time, diagnosis, and treatment regimen. If additional information or clarifications were needed, the authors of the study were contacted. In case the same results of an RCT had been published in more than one article, either the one with the best quality or the most recent one was included in our analysis. In case more than one article reported the results of the same RCT at different follow-ups, these were all included unless there was one article having all the needed data. Risk of bias of included RCTs was assessed by using the Cochrane collaboration tool 14.

Data analysis

Our primary analysis was the estimate of the incidence rate ratio (IRR) of death by pooling data from all studies, across drugs and diseases. We calculated the IRR with 95% confidence interval (CI) for receiving 5 injections using the mean number of injections in each study arm as an exposure, with studies as a random effect; we also presented IRRs
for a single injection and for 10 injections for illustrative purposes. To avoid spurious findings, we planned to explore non-linear associations only if a significant linear effect was detected. We used mixed regression models to investigate the relationship between the mean number of injections received in each study arm and all-cause mortality, with studies as random effects. This statistical technique allowed us to include trials with more than two-arms and trials comparing different regimens with no sham group. This also allowed us to include trials in which rescue anti-VEGF treatment was delivered in a sham arm after the randomization period ended, typically in year 2 or earlier in trials on RVO. Since death was rare in most studies, with no events reported in smaller studies, we used Poisson regression to fit mixed models exploring the association between the number of injections and mortality rate.

We conducted separate analyses in subgroups of study drug and disease to explore potential differences in the linear effect of the number of injections. We decided not to fit complex models with interaction terms to test any differences between subgroups, since this could cause bias in a relatively small dataset with very rare events, particularly for RVO.

We presented study-arm level mortality data in forest plots, including a meta-analysis with the overall risk of death for each disease at 12 and 24 months, for descriptive purposes. Stata software (version 16.2, StataCorp, College Station, TX, USA) was used for meta-analyses. Two-tailed $P < .05$ was considered significant.

**Results**

**Study selection**

The study selection flow diagram is shown in Figure 1. The electronic search yielded a total of 7,874 records, of which 2,851 were duplicates. Of the remaining 5,023 records, 4,861 were removed after title and abstract screening. One hundred sixty-two potentially
eligible articles were full-text evaluated, of which 95 were ruled out. A total of 67 articles reporting the results of 52 unique RCTs met the eligibility criteria and were included in this analysis. List of included studies, study characteristics and quality assessment (eFigures 1 and 2) are available online in supplemental material.

Number of injections and all-cause mortality

There were 134 deaths out of 13,099 patients (1.02%) in 46 studies providing data at 12 months. At 24 months, 326 deaths out of 9,691 participants (3.36%) were recorded in 18 studies. The median of the study-level average injections was 7.1 (IQR 3.3 – 10.1) at 12 months and 11.6 (IQR 5.9 – 20.6) at 24 months.

Supplemental eFigures3-8 present raw mortality data for each study and study arm at 12 and 24 months, together with the average number of injections and study drug. Table 1 also shows the results of analyses conducted in different subgroups of diagnosis and drug type.

We found no significant overall increase in mortality in the primary analysis pooling all data across indications and drugs (linear effect of 5 injections: IRR, 95%CI) both at 12 months (1.16, 0.87-1.53; p=0.31) and at 24 months 1.05 (0.95-1.15; p=0.34). Given the observed mortality in the control arm of about 1% and 3.5% at 12 and 24 months, respectively, the upper limit of the 95%CI of our IRR estimates rules out an increase in mortality above 0.50%. For descriptive purposes, we also present IRRs for 1 and 10 injections: 1.03 (95% CI: 0.97-1.09) and 1.34 (95% CI: 0.76-2.35), respectively.

Overall mortality was about 1% at 12 months when subgroups by disease and drug were considered, except in RVO studies, which included a lower-risk population (0.03% mortality). A similar overall risk of death was observed at 24 months, with a mortality of about 3% in most subgroups. A lower mortality was found in RVO studies (1.4%), while
bevacizumab studies had a higher mortality (6%) with respect to other drugs. These divergent findings are likely to reflect differences in eligibility criteria of the included studies and should not have influenced our overall analysis, which took into account within-study correlation of data.

Table 1 shows that no significant mortality increase was associated with an increasing mean number of injections for each study drug subgroup. No significant relationship was also detected for disease subgroups, with two exceptions. The apparently protective effect of a linear increase of mean number of injections in RVO at 24 months was likely related to the fact that only two studies with 9 deaths were included, and an apparent reverse effect was found in the Copernicus trial. On the other hand, an increased risk of death of marginal significance was found in DME studies (IRR 1.17, 1.02-1.33, p=0.03) based on 5 studies with 74 deaths (Table 1, Figure 1).

Discussion

This study sought to explore whether a more intense treatment with intravitreal anti-VEGF agents could be associated with a higher mortality. Our analyses demonstrated no relationship between the number of anti-VEGF injections and overall death rate. However, subgroup analysis revealed that an increasing number of anti-VEGF injection seemed to be associated with a higher death risk in DME patients at 24 months.

The issue of systemic safety of intravitreal anti-VEGF therapy has long been discussed and the efforts made to address it appear still inconclusive. On the one hand, randomized controlled trials seem to not be powered enough to assess the safety of uncommon events such as mortality. On the other hand, real-world data are controversial. Hanhart et al. demonstrated a higher long-term mortality in patients receiving intravitreal bevacizumab for AMD compared with non-AMD age- and gender-matched controls. The same authors showed
that in patients diagnosed with a stroke or a transient ischemic attack the mortality risk within 3 months from the cerebrovascular event was six-fold higher if they were exposed to intravitreal bevacizumab. Dalvin et al. demonstrated a higher death risk in AMD patients treated with anti-VEGF compared with wet-AMD patients of the pre anti-VEGF era. Other reports did not reveal a higher risk for cardiovascular accidents and death in patients receiving intravitreal anti-VEGF therapy.

A possible reason for such questionable evidence is that estimates provided by real-world studies might be easily biased when relative risk of low-frequency events is likely to be confounded by multiple variables. In this scenario, meta-analysis studies have tried to overcome the limited power obtained in individual RCTs. However, their results have been conflicting and affected by imprecision of effect estimates. Several meta-analyses showed no evidence of increased risk for cardiovascular accident and/or mortality associated with intravitreal anti-VEGF therapy. Ueta et al. demonstrated a higher risk for cerebrovascular accident in AMD patients treated with 0.5 mg ranibizumab compared with those receiving both sham and a lower dosage.

In a recent meta-analysis of RCTs comparing anti-VEGF treatment versus controls, we found no significant increase in mortality rates associated with anti-VEGF therapy, but a warning signal of increased mortality risk associated with a more intense treatment frequency was shown. Thus, we decided to conduct the present meta-analysis specifically aimed at investigating whether a different number of anti-VEGF injections could be associated with a higher mortality. Given this purpose, the eligibility criteria of the present study are different compared with our previous one: randomized trials enrolling arms with different intensity of intravitreal anti-VEGF therapy have been included in the present meta-analysis, while our previous one included only trials comparing anti-VEGF treatment with an untreated control group. As a result, the present study is based on a
new and larger dataset, including 52 randomized trials with a total of more than 13,000 patients at 1 year and almost 10,000 patients at 2-year follow-up. Our previous study found a significant linear trend with increasing number of injections in the treated vs control groups (Odds Ratio 1.12, 95%CI: 1.04-1.22 for one injection). The present review has used a different approach (arm-based instead of study-based) and a different analytic technique (Poisson mixed model meta-regression) and effect measure (IRR instead of odds ratio), with no categorization at the study-level. The results of these new analyses are more precise and provide a message of reassurance on anti-VEGF safety in the overall population (IRR: 1.03, 95%CI: 0.97-1.09, for one injection). However, a warning signal in DME patients at 24 months persisted, even with an increase by 50% of total patients.

The issue of a possible influence of treatment frequency on systemic safety is of great clinical relevance. In clinical practice, management of AMD, DME and RVO has changed. Fixed regimen and treat&extend protocols have been shown more effective compared with pro re nata regimen. The tendency is to schedule patients for injections on a long-term period, with clinic assessments at specific time-points. This attitude helps to reduce the number of in-clinic follow-up visits, which represent a significant burden for overwhelmed medical retina units. As a result, the number of injections steadily goes up and an average of 13 anti-VEGF injections are usually administered over two years for both AMD and DME patients.

Our analysis yielded an IRR of 1.16 and 1.05 when evaluating the influence of an increasing number of injections (linear effect calculated for 5 injections) on mortality at 12 and 24 months, respectively. These findings seem to rule out a relationship between treatment intensity and the risk of death. Furthermore, the estimates provided by our analyses excluded an increase in death risk above 0.50% both at 12 and at 24 months in low-risk patients with an overall risk of about 1% and 3.5%, respectively.
Subgroup analyses showed that the type of drug had no influence on our estimates, even though a 6% raw risk of death was found in bevacizumab studies at 24 months. Some doubts about differences in safety profile amongst anti-VEGF drugs have been raised. Ranibizumab has a shorter half-life compared with both bevacizumab and aflibercept. Furthermore, ranibizumab produces a smaller reduction of circulating free VEGF compared with the two other agents. Theoretically, these features should make ranibizumab less likely to cause potential systemic side effects. However, our higher mortality rate at 24 months in bevacizumab studies seems to reflect differences in inclusion criteria of the selected studies, i.e. with more high-risk patients, and had no influence on the overall analysis.

We found a lower death rate in RVO studies, with an apparent protective effect of the increasing number of injections at 24 months (IRR=0.09, 95% CI= 0.02-0.51). These findings should be cautiously interpreted because only two studies were included in the RVO subgroup at 24 months and figures had been mainly influenced by the Copernicus study, which recorded 4 deaths in the sham crossing-over arm versus no death in the aflibercept arm.

Importantly, an increased death risk was associated, even if marginally, with a more intense treatment frequency in patients with DME diagnosis at 24 months (IRR= 1.17, 95% CI=1.02-1.33). Diabetic patients feature a higher risk for cardiovascular accidents compared with non-diabetic ones, so that diabetes could be considered an equivalent of coronary heart disease. In diabetic patients the presence of DME is associated with a 2-fold higher rate of hospitalization for stroke and myocardial infarction. Systemic safety of intravitreal anti-VEGF therapy in patients with DME has been questioned. In particular, Avery et al. demonstrated a higher mortality in DME patients receiving a prolonged and intensive intravitreal anti-VEGF treatment. In a meta-analysis we recently published on mortality risk in patients treated with anti-VEGFs, DME diagnosis was associated with a
higher death rate compared with AMD diagnosis. Conversely, Cochrane meta-analyses on DME did not reveal a significant difference in mortality rate between intravitreal anti-VEGF therapy and controls. The present meta-analysis seems to corroborate the findings of higher risk in DME patients. However, the evidence is limited by a marginal significance with a 95% CI limit close to null (1.02-1.33). Furthermore, DME patients that need for an intensive and prolonged intravitreal anti-VEGF therapy are likely to present a poor metabolic control, with high level of glycosylated hemoglobin and impaired renal function. A higher mortality in this category of patients could be related to some extent to this complex systemic condition.

The following limitations need to be acknowledged. First, we investigated a rare event, such as mortality. This implied that many of the included trials reported no event, not being powered to assess this outcome. Meta-analyses are supposed to overcome this issue, however estimates might be imprecise or unstable when analyses restricted to specific subgroups, e.g. RVO, were conducted.

Randomized clinical trials included in this meta-analysis were characterized by strict eligibility criteria. Most of these studies excluded patients with a history of cardiovascular accidents, such as stroke and myocardial infarction. Thus, our findings cannot be extrapolated to the general population and should be interpreted cautiously in patients at high cardiovascular risk.

Most included studies were sponsored by pharmaceutical companies, which might be a risk for bias. Moreover, some trials might not consider a drug-related adverse effect an event that occurred 1 month or longer after drug injection, as was the case of the Intravitreal Aflibercept Injection in Vision Impairment Due to DME (VIVID-DME) trial and the Study of Intravitreal Aflibercept Injection (IAI; EYLEA®; BAY86-5321) in Patients With Diabetic Macular Edema (VISTA DME). However, this does not represent a real limitation for the outcome we explored, because all-cause mortality is unlikely to be biased.
Finally, we ran analyses on tabulated data. Individual data were not available and individual clinical variables, which may have an influence on mortality, could not be investigated. Nonetheless, meta-analysis studies are assumed to provide a higher level of evidence compared with individual trials.

The present meta-analysis showed that treatment intensity with intravitreal anti-VEGF agents has no significant influence on mortality, supporting a message of reassurance over safety concerns related to this sight-saving treatment. A warning signal of higher risk associated with an increasing number of injections seems to concern DME patients in the long-term. However, the evidence of this study is applicable to a low-risk population because most of included trials ruled out patients with history of cardiovascular events. Further studies based on real world data are warranted to corroborate our findings and to explore this issue in patients at high cardiovascular risk.

Acknowledgments

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Reference


Randomized Clinical Trial. JAMA Ophthalmol 2019;137:382–389. Available at:


Figure legends

Figure 1: Flow diagram of the study selection process.

Figure 2: Incidence rate ratio, shown as effect size (ES) with 95% confidence intervals (CI) for receiving 5 more injections at 12 and 24 months in different subgroups of diagnosis and drug type. Cumulative incidence (CumInc) at 1 and 2 years (deaths/total) is also shown.

List of elements included in online Supplemental Material.
-Characteristics of included studies
-Quality assessment
-Reference of included studies
-eTable1: PRISMA checklist.
-eTable 2: Search strategy.
-eFigure1: Risk of bias graph.
-eFigure2: Risk of bias summary.
-eFigure3: Raw data at study-arm level for age related macular degeneration (AMD) studies with data at 12 months.
- **eFigure4**: Raw data at study-arm level for diabetic macular edema (DME) studies with data at 12 months.

- **eFigure5**: Raw data at study-arm level for retinal vein occlusion (RVO) studies with data at 12 months.

- **eFigure6**: Raw data at study-arm level for age related macular degeneration (AMD) studies with data at 24 months.

- **eFigure7**: Raw data at study-arm level for diabetic macular edema (DME) studies with data at 24 months.

- **eFigure8**: Raw data at study-arm level for retinal vein occlusion (RVO) studies with data at 24 months.
ICMJE DISCLOSURE FORM

Date: 12/19/2021

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Manuscript Title: Frequency of intravitreal anti-vascular endothelial growth factor injections and risk of death: a systematic review with meta-analysis

Manuscript Number (if known): ORET-D-21-00606R1

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3. Royalties or licenses
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Please place an “X” next to the following statement to indicate your agreement:

☐ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

[Signature]
Table 1. Incidence rate ratio (IRR, 95%CI, per 5 more injections) at 12 and 24 months in different subgroups of diagnosis and drug type.

<table>
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<th>Covariate</th>
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<th>24 months</th>
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<td>Studies</td>
<td>Deaths/Total (%)</td>
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<tr>
<td>Overall</td>
<td>46</td>
<td>134/13,099 (1.02%)</td>
</tr>
<tr>
<td>AMD</td>
<td>20</td>
<td>99/7,404 (1.34%)</td>
</tr>
<tr>
<td>DME</td>
<td>12</td>
<td>27/3,115 (0.87%)</td>
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<td>RVO</td>
<td>14</td>
<td>8/2,580 (0.03%)</td>
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<td>Aflibercept</td>
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<td>41/3,673 (1.12%)</td>
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<td>64/7,466 (0.86%)</td>
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<tr>
<td>Bevacizumab</td>
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<td>30/1,960 (1.53%)</td>
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Footnote: CI= confidence intervals; IRR= incidence rate ratio; AMD= age-related macular degeneration; DME: diabetic macular edema; RVO: retinal vein occlusion.
PRISMA 2009 Flow Diagram

Records identified through database searching (n = 7874) (PubMed, Embase, Cochrane Library, clinicaltrials.gov)

Duplicates removed (n = 2851)

Records screened (n = 5023)

Records excluded (n = 4861) due to title/abstract irrelevant for this study

Full-text articles assessed for eligibility (n = 162)

95 Full-text articles excluded:
- Other diagnosis (n = 19)
- Other anti-VEGF agent (n = 9)
- Follow-up < 1 year/ > 3 years (n = 28)
- Non randomized (n = 18)
- No sham group/no different treatment regimen (14)
- Enrolling both eyes of the same patient (6)
- No safety data (1)

Articles included in qualitative synthesis (n = 67)

Articles included in quantitative synthesis (meta-analysis) (n = 67)


For more information, visit www.prisma-statement.org.
Précis

This study demonstrated no significant relationship between the number of anti-vascular endothelial growth factor (anti-VEGF) injections and mortality. However, a signal of higher risk was found in patients receiving anti-VEGF therapy for diabetic macular edema.