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Incidence, Risk Factors, and Outcomes of Rhegmatogenous Retinal Detachment after Intravitreal Injections of Anti-VEGF for Retinal Diseases

Data from the Fight Retinal Blindness! Registry

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Purpose: To report the estimated incidence, probability, risk factors, and 1-year outcomes of rhegmatogenous retinal detachment (RRD) in eyes receiving intravitreal injections (IVTs) of VEGF inhibitors for various retinal conditions in routine clinical practice.

Design: Retrospective analysis of data from a prospectively designed observational outcomes registry: the Fight Retinal Blindness! project.

Participants: Eyes of patients starting IVTs of VEGF inhibitors (ranibizumab, aflibercept, or bevacizumab) for neovascular age-related macular degeneration, diabetic macular edema, or retinal vein occlusion from January 1, 2006, to December 31, 2020. All eyes that developed RRD within 90 days of IVTs were defined as cases with RRD and were matched with control eyes.

Methods: Estimated incidence, probability, and hazard ratios (HRs) of RRD were measured using Poisson regression, Kaplan–Meier survival curve, and Cox proportional hazards models. Locally weighted scatterplot smoothing curves were used to compare visual acuity (VA) between cases and matched controls.

Main Outcome Measures: Estimated incidence of RRD.

Results: We identified 16 915 eyes of 13 792 patients who collectively received 265 781 IVTs over 14 years. Thirty-six eyes were reported to develop RRD over the study period. The estimated incidence (95% confidence interval [CI]) per year per 1000 patients and per 10 000 injections was 0.77 (0.54–1.07) and 1.36 (0.95–1.89), respectively. The probability of RRD did not significantly increase at each successive injection ($P = 0.95$) with the time of follow-up. Older patients (HR [95% CI] = 1.81 [1.21–3.62] for every decade increase in age, $P < 0.01$) were at a higher risk of RRD, whereas patients with good presenting VA (HR [95% CI] = 0.85 [0.70–0.98] for every 10-letter increase in VA, $P = 0.02$) were at a lower risk. Neither the type of retinal disease ($P = 0.52$) nor the VEGF inhibitor ($P = 0.09$) was significantly associated with RRD risk. Cases with RRD lost 3 lines of vision on average compared with the prior RRD VA and had significantly fewer injections than matched controls over the year after the RRD.

Conclusions: Rhegmatogenous retinal detachment is a rare complication of VEGF inhibitor IVT in routine clinical practice with poor visual outcomes at 1 year. *Ophthalmology Retina 2022;■:1–10 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Intravitreal anti-VEGF agents are widely used for exudative retinal diseases, such as neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO).[1–4] The intravitreal injection (IVT) procedure is relatively safe, but serious ocular complications may occur, including retinal tear, rhegmatogenous retinal detachment (RRD), cataract formation, and endophthalmitis, the last being the most feared.[5]

Rhegmatogenous retinal detachment is a common ocular condition affecting 5 to 20 people in 100 000 each year.[6] Predisposing factors are mainly older age, male sex, myopia, cataract surgery, trauma, posterior vitreous

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detachment, and vitreoretinal changes.[6–8] Although not well-defined in the literature, RRD after VEGF inhibitor IVT seems to be uncommon. The rate per injection is estimated to be between 0.008% and 0.023% from previous randomized clinical trials and retrospective monocenter studies.[9–13] Most previous studies have reported the incidence as a rate "per IVT." However, the follow-up time and number of IVTs vary between each patient and according to the type of drugs and retinal diseases. The individual risk of RRD may grow over time with repeated IVTs. To report the IVT RRD risk, it may be more clinically relevant to report RRD incidence "per patient per year" and probability "per patient" with time or number of injections. Few studies have investigated the risk factors associated with RRD after IVTs or the long-term outcomes of this complication and none have included a control group.[12,13]

This study aimed to explore the estimated incidence of RRD after IVT of VEGF inhibitors for various retinal diseases in routine clinical practice over a 14-year study period. The secondary objective was to assess the probability with time or injections and baseline risk factors of RRD and evaluate the 12-month visual and treatment outcomes of eyes with RRD, including a comparison between cases with RRD and their matched controls.

Methods

Design and Setting

This was a retrospective analysis of treatment-naïve eyes that had received intravitreal VEGF inhibitors for various retinal diseases in routine clinical practice tracked in the prospectively designed observational database—The Fight Retinal Blindness! Registry.[14] Centers participating in this analysis were from Australia, France, Ireland, Italy, Netherlands, New Zealand, Spain, Singapore, Switzerland, and the United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Mater Private Hospital Institutional Review Board in Dublin, Ireland, the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, the Caldicott Guardian at the Royal Free London NHS Foundation Trust, the SingHealth Singapore, the Spanish Institutional Review Board (Comité Etico de Investigación Medica, Hospital Clínic de Barcelona, Spain), and the Cantonal Ethics Committee Zurich. Because of its noninterventional character, approval of the use of the registry was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands. All patients gave consent. Informed consent (opt-in consent) was sought from patients in France, Ireland, Italy, Netherlands, Spain, Singapore, Switzerland, and the United Kingdom. Ethics committees in Australia and New Zealand approved the use of "opt-out" patient consent. This study adhered to the tenets of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational studies in Epidemiology statements for reporting observational studies.[15]

Data Sources and Measurements

The Fight Retinal Blindness! registry system collected data from each clinical visit, including visual acuity (VA) measurement (letters read on a logarithm of the minimum angle of resolution VA chart, best of uncorrected, corrected, and pinhole), treatment given, if any, and ocular adverse events. Demographic characteristics (age and sex), initial diagnosis (AMD, DME, or RVO), and whether the eye received prior treatment (including cataract surgery and vitrectomy) were recorded at the baseline visit. Treatment decisions, including the choice of VEGF inhibitor and visit schedule, were at the physician's discretion in consultation with the patient, thereby reflecting daily clinical practice.

Documentation of RRD was recorded as follows at the discretion of the ophthalmologist. Rhegmatogenous retinal detachment included all cases of RRD occurring < 90 days after the last IVT. Data on RRD initial clinical characteristics and severity and types of management were not recorded in the Fight Retinal Blindness! database. Eyes with RRD were excluded if they had a prior history of RRD in the affected eye at the baseline visit and recent intraocular surgery (< 90 days, such as cataract surgery or vitrectomy) in the affected eye between the last IVT and the development of RRD.

The VA at RRD was defined as the VA during the visit RRD was recorded, whereas the VA prior RRD was defined as the VA during the visit immediately before the RRD visit. The VA loss (change) at RRD was the VA prior RRD minus the VA at RRD. The VA loss (change) from prior RRD was defined as the VA at the 1-year follow-up or that observed at the last recorded visit minus VA prior RRD. The VA loss (change) from RRD was considered the VA at the 1-year follow-up or that observed at the last recorded visit minus VA at RRD.

Patient Selection and Groups

Treatment-naïve eyes tracked by the Fight Retinal Blindness! outcome registry that started IVTs of VEGF inhibitors (ranibizumab [0.5-mg Lucentis, Genetech Inc/Novartis], aflibercept [2-mg Eylea, Regeneron Inc/Bayer] or bevacizumab [1-mg Avastin, Genetech Inc/Roche]) for neovascular AMD or DME or macular edema secondary to RVO from January 1, 2006, to December 31, 2020, were considered for the analysis. Eyes with a prior history of IVIs, laser, or surgery for their retinal disease or a history of RRD repair at baseline visit were excluded from this analysis.

Outcomes

The main outcome was the estimated incidence of RRD over the study period. The secondary outcomes were the probability of RRD with time or injections and RRD development hazard ratios (HRs). The other outcomes of interest were the change in VA, time to the first IVT after RRD, and the number of IVTs received at 12 months after RRD, including a comparison between cases and their matched controls.

To study the estimated incidence, rate, and HRs, all cases of RRD were recorded, regardless of their follow-up. For secondary outcomes related to outcomes after the diagnosis of RRD, RRD had to occur between January 1, 2010, and December 31, 2019, to allow the possibility of having ≥ 1 year of follow-up from the time of RRD. We included 5 controls receiving IVT per case matched with their respective cases on the following characteristics: baseline VA, duration before RRD, VA before RRD, type of retinal disease, and the number of IVTs before RRD. Eyes that completed ≥ 335 days of follow-up after RRD were defined as "completers." The "noncompleters" were defined as eyes that did not complete ≥ 335 days of follow-up after RRD.

Statistical Analysis

Descriptive data were summarized using the mean (standard deviation), median (first and third quartiles), and percentages where

Table 1. Incidence and probability of RRD Over the Study

	RRD
Cases, n	36
Study period, yrs	14
Injections along the study period, n	264 272
Patients along the study period, n	13 690
Females, n (%)	7879 (58)
Age, mean yrs (SD)	77 (10)
Incidence per year per 1000 patients (95% CI)*	0.77 (0.54−1.07)
Incidence per 10 000 injections (95% CI)*	1.36 (0.95−1.89)
Cases and rate by type of VEGF inhibitors, case/injections (%)†	
Bevacizumab	4/45 902 (0.009)
Ranibizumab	21/117 093 (0.018)
Aflibercept	11/100 368 (0.011)
Probability per patient following number of injections %‡	
10th injection	0.152
20th injection	0.238
30th injection	0.262
40th injection	0.535
50th injection	0.539
Case and rate by type of retinal disease, case/injections (%)§	
Neovascular AMD	26/230 265 (0.011)
DME	7/15 859 (0.044)
Macular edema secondary to RVO	3/18 148 (0.017)
Time (days) to rhegmatogenous retinal detachment, median (Q1, Q3)	756 (337, 1395)
Number of injections until rhegmatogenous retinal detachment, median (Q1, Q3)	11 (5, 20)

AMD = age-related macular degeneration; CI = confidence interval; DME = diabetic macular edema; RRD = rhegmatogenous retinal detachment; RVO = retinal vein occlusion; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
*Calculated using the Poisson test.
†Type of VEGF inhibitor received before the diagnosis of RRD. *P* value among the 3 drugs = 0.23.
‡The probability of RRD per patient did not significantly increase with each successive injection ($P = 0.95$).
§*P* value among the 3 types of retinal diseases ($P = 0.003$); pairwise comparisons with Holm−Bonferroni adjustment for multiple comparisons: AMD vs. DME ($P = 0.006$), AMD vs. RVO ($P = 0.78$), and DME vs. RVO ($P = 0.37$).

appropriate. The estimated incidences of RRD per year per 1000 patients and per 10 000 injections during the study period were evaluated using the Poisson test. Kaplan−Meier curves were used to estimate the probability of RRD per patient by the number of injections received and the length of follow-up. Cox proportional hazards model was used to relate RRD development to the following time-independent covariates: age, sex, VA and type of retinal disease, lens status, and type of VEGF inhibitors at baseline.

Locally weighted scatterplot smoothing regression was used to visualize longitudinal visual outcomes over 12 months between eyes of cases with RRD and matched control eyes. Visual and treatment outcomes were compared between eyes of cases with RRD and matched control eyes using analysis of variance, *t* tests, and chi-square tests where appropriate. Kaplan−Meier survival analyses were used to plot the time to the first injection after RRD surgery.

A *P* value of 0.05 was considered statistically significant. *P* values from pairwise comparisons between the type of anti-VEGF agent and retinal disease groups were adjusted for using the Holm−Bonferroni correction method. All analyses were conducted using R software version 3.6.3 (http://www.R-project.org/).

Results

Study Population

This study included 16 792 eyes (13 690 patients) collectively receiving 264 272 IVTs over 14 years between January 1, 2006, and December 31, 2020. The number of eyes at each selection criterion is shown in Figure S1 (available at www.ophthalmologyretina.org). Sixteen percent of eligible eyes completed ≥ 5 years of follow-up, and 2% completed ≥ 10 years of follow-up. We recorded 36 RRDs during the study period, of which 32 eyes developed RRD before December 31, 2019 to allow the possibility of having ≥ 1 year of follow-up from the time of RRD. Twenty-four (75%) eyes completed 12 months of follow-up after RRD.

Incidence and Probability of RRD after IVT

The estimated incidence (95% confidence interval [CI]) per year per 1000 patients and per 10 000 injections was 0.77 (0.54−1.07) and 1.36 (0.95−1.89), respectively, over the study period (Table 1). The number of RRD per injections was not significantly different between drugs with 0.009%, 0.018%, and 0.011% for bevacizumab, ranibizumab, and aflibercept, respectively ($P = 0.23$) (Table 1). The number of cases per injections tended to be more frequent in eyes treated for DME than in eyes treated for neovascular AMD (0.044% vs. 0.011%, $P = 0.006$) but was not significantly different between RVO vs. DME (0.017% vs. 0.044%, $P = 0.37$) and neovascular AMD vs. RVO (0.011% vs. 0.017%, $P = 0.78$) (Table 1).

Kaplan−Meier estimates of the probability of RRD by the length of follow-up and the number of injections are shown in Figure 1. The RRD probability was 0.2% at 2 years, 0.3% at 4

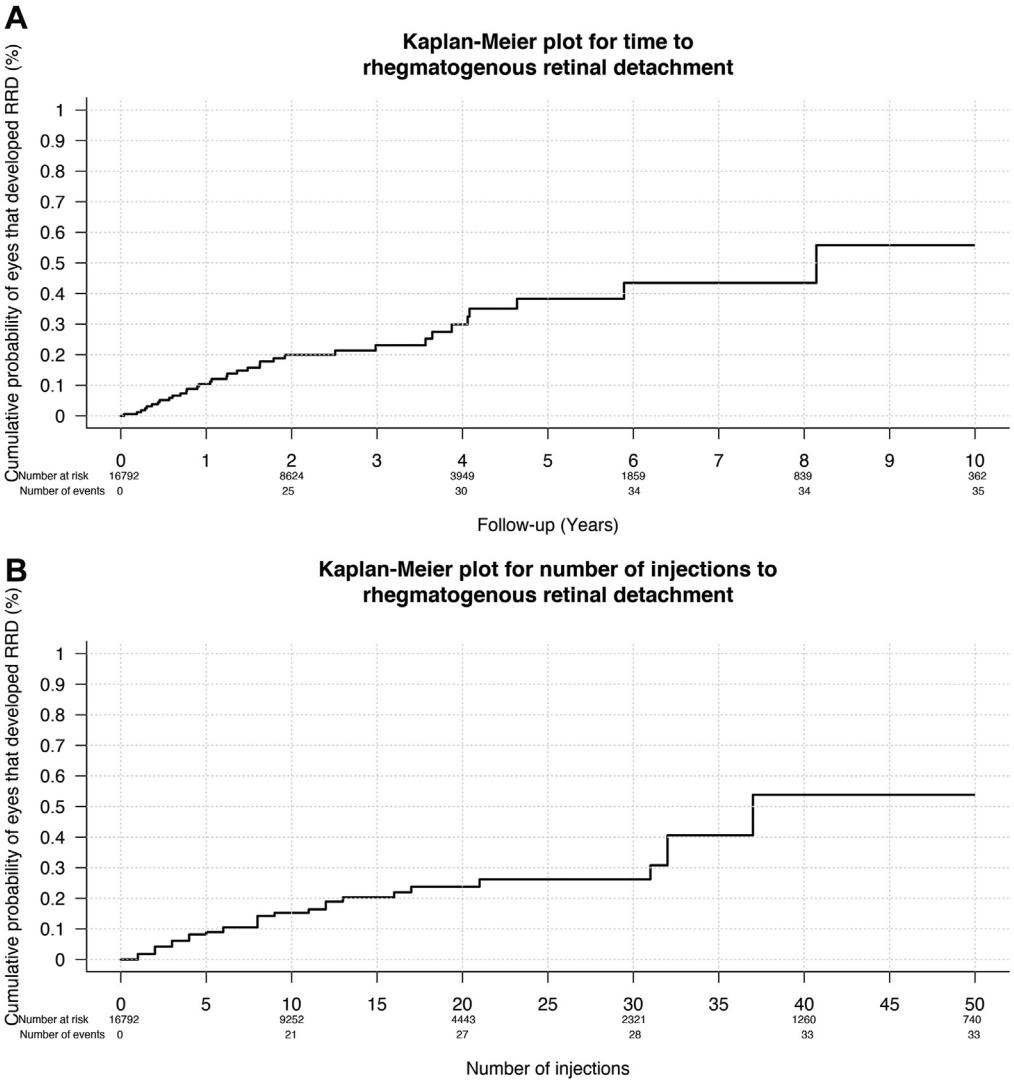

Figure 1. Kaplan–Meier curve of the probability of rhegmatogenous retinal detachment (RRD) by **A,** the length of follow-up and **B,** the number of injections received.

years, 0.4% at 6 years, 0.4% at 8 years, and 0.6% at 10 years of follow-up (Fig 1A). The probability of RRD was 0.15% at 10 injections, 0.24% at 20 injections, 0.26% at 30 injections, 0.54% at 40 injections, and 0.54% at 50 injections. The probability of RRD did not significantly increase at each successive injection ($P = 0.95$) with the time of follow-up (Table 1; Fig 1B). The median (Q1, Q3) time and injections until RRD were 756 (337, 1395) days and 11 (5, 20) injections (Table 1).

Cox proportional hazards model was used to identify baseline covariates predictive of RRD development in eyes receiving VEGF inhibitors (Table 2). The baseline age (HR [95% CI] = 1.81 [1.21–3.62] per 10 years of age; $P < 0.01$) and VA (HR [95% CI] = 0.85 [0.70–0.98] per 10-letter score; $P < 0.02$) were associated with RRD development over the study (Table 2). The incremental likelihood of developing RRD decreased by 15% with each additional 10 ETDRS letter score (2 lines) at the start of the treatment. Sex, lens status, and type of retinal disease were not significantly associated with RRD development. The type of VEGF inhibitors tended to be associated with RRD; however, we did not identify any significant pairwise comparisons (Table 2).

Outcomes of RRD after IVT

The visual outcomes of cases with RRD and their comparison with matched control eyes are described in Table 3 and Figure 2. The mean (95% CI) change in VA from prior RRD was −15 (−25, −5) letters at 12 months after RRD. Forty-four percent and 31% of eyes with RRD had at least 2- and 3-line visual loss from prior RRD at 12 months, respectively. One-third of the eyes with RRD recovered their VA prior RRD at 12 months, whereas two-third of the matched control eyes maintained their vision during the same period ($P < 0.01$) (Table 3).

The median (Q1, Q3) number of injections over the 12 months after RRD was significantly lower in eyes with RRD than in matched control eyes (3 [0, 7] vs. 6 [3, 8]; $P = 0.02$), whereas the median number of visits was not significantly different ($P = 0.32$) (Table 3). At least 1 IVT was given to 75% of cases with RRD 12

Table 2. Mixed-Effects Cox Proportional Hazard Regression Model for the Development of RRD

	Development of RRD	
Covariates (Reference if Categorical)	*HR (95% CI)*	P *Value*
Sex (female)		0.085
Male	1.83 (1.14–2.53)	
Age at baseline (every 10 years of age)	1.81 (1.21–3.62)	<0.01*
VA at baseline (every 10-letter score)	0.85 (0.70–0.98)	0.020*
Lens status (phakic)		0.69
Pseudophakia	1.20 (0.20–2.20)	
Type of VEGF inhibitors (bevacizumab)		0.035*,†
Aflibercept	1.61 (0.31–2.91)	
Ranibizumab	3.11 (2.03–4.19)	
Type of retinal disease (neovascular AMD)		0.52
DME	1.00 (0.77–1.82)	
Macular edema secondary to RVO	0.52 (0.05–2.06)	

Model Random Effects	**Standard Deviation**	**Variance**
Practitioner/patient	1.3	1.7
Practitioner only	0.4	0.13

AMD = age-related macular degeneration; CI = confidence interval; DME = diabetic macular edema; HR = hazard ratio; RRD = rhegmatogenous retinal detachment; RVO = retinal vein occlusion; VA = visual acuity.
*Significant *P* values.
†Pairwise comparisons with the Holm–Bonferroni adjustment for multiple comparisons: bevacizumab vs. aflibercept ($P = 0.75$), bevacizumab vs. ranibizumab ($P = 0.10$), aflibercept vs. ranibizumab ($P = 0.34$).

months after its development with a median (Q1, Q3) time to the first injection of 69 (34, 177) days (Fig 3A). Eighty-three percent and 50% of eyes with neovascular AMD and DME, respectively, had ≥ 1 IVT 12 months after RRD, whereas no eye with RVO had a single injection during the same period. However, there was no significant difference in the probability of resuming intravitreal

Table 3. Outcomes at 12 Months after RRD Compared with a Matched Control Group without RRD

	Cases with RRD	**Matched Controls***	***P***
All eyes, n	32	160	
12-month completers, n	28	160	
VA logMAR letters, mean (SD)			
Baseline	53 (24)	55 (22)	0.57
Prior RRD	59 (23)	63 (21)	0.43
At RRD	38 (29)	-	
Final (at 12 mos from RRD)†	45 (29)	64 (19)	<0.01‡
VA change at RRD letters, mean (SD)	−22 (31)	-	
VA change from RRD at 12 mos letters, mean (95% CI)	+7 (−4, 19)	+2 (0, 4)	0.09
VA gain from RRD at 12 mos, %			
≥5 letters	38	30	0.53
≥10 letters	25	15	0.26
≥15 letters	22	9	0.08
VA change from prior RRD at 12 mos letters, mean (95% CI)	−15 (−25, −5)	+2 (0, 4)	<0.01‡
VA loss from prior RRD at 12 mos, %			
<5 letters	47	76	<0.01‡
≥5 letters	53	24	<0.01‡
≥10 letters	44	12	<0.01‡
≥15 letters	31	5	<0.01‡
VA prior RRD recovered at 12 mos, %	31	63	<0.01‡
Injections 12 mos after RRD, median (Q1, Q3)	3 (0, 7)	6 (3, 8)	0.02‡
Visits 12 mos after RRD, median (Q1, Q3)	10 (7, 12)	9 (7, 11)	0.34

CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; Q1 = first quartile; Q3 = third quartile; RRD = rhegmatogenous retinal detachment; SD = standard deviation; VA = visual acuity.
*Controls are matched for baseline VA, sex, time duration before RRD, last VA recorded before RRD, the number of intravitreal injections before RRD, and type of retinal disease.
†Last observation carried forward for noncompleters.
‡Significant *P* values.

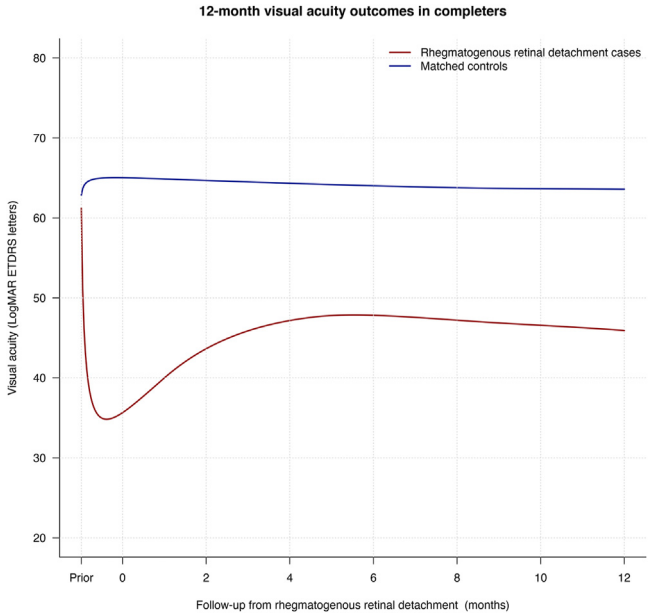

Figure 2. Locally weighted scatterplot smoothing curve regression of mean visual acuity (VA) after the onset of rhegmatogenous retinal detachment (RRD). Matched cohort consisting of 5 controls per case matched with their respective cases on the following characteristics: baseline VA, sex, duration before RRD, last VA recorded before RRD, the number of intravitreal injections before RRD, and type of retinal disease. logMAR = logarithm of the minimum angle of resolution.

treatment according to the type of retinal disease (log-rank test $P = 0.30$) (Fig 3).

Discussion

The Fight Retinal Blindness! registry allowed us to assess the estimated incidence, probability, risk factors, and visual outcomes of RRD within 3 months of an IVT of VEGF inhibitor for various retinal diseases over 14 years in routine clinical practice. Our study found that the rate of RRD "per IVT" (0.014%, 1 RRD per 7383) was similar to that reported in the previous studies (Table 4).[1,4,9,10,12,13,16–18] The rates of RRD "per IVT" in randomized clinical trials were estimated to be 1 RRD per 1250 IVTs (0.08%) in the VEGF inhibition Study in Ocular Neovascularization trial,[16] 1 per 8500 IVTs (0.012%) in the minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of AMD trial,[1] 1 per 8223 IVTs (0.012%) in the RISE and RIDE trial,[9] and 1 per 1833 IVTs (0.054%) of bevacizumab and ranibizumab in the Comparison of Age-Related Macular Degeneration Treatments Trials.[17] No RRD was reported in 3282 IVTs of ranibizumab in the efficacy and safety of ranibizumab injection in patients with macular edema secondary to central RVO trial.[10] The reported RRD rates in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD study were 1 per approximately 13 000 IVTs (0.008%).[4] Retrospective studies have found varying results from 0.0084% to 0.013%.[12,13,18] Our findings confirmed that the risk of RRD "per IVT" is low in routine clinical practice (Table 4).

Our study group believes that it is crucial to report the incidence "per patients per year" and the probability "per patient with time or number of injections" to better evaluate RRD risk after VEGF inhibitor IVT. Depending on the retinal diseases, response to treatment, and patient compliance, 1 patient may have received up to 60 IVTs over 10 years, whereas another patient may only receive 5 injections over 2 years, which may skew the rate of RRD per patients and IVT. Overall, we found < 1 RRD after IVT per year per 1000 treated patients in our database study. We have not found similar data in the literature for comparison. Previous studies have found conflicting RRD rates "per patient," with time from 1 RRD per 186 to 1 RRD per 1842 treated patients because of varying follow-up times.[12,19,20] These conflicting findings highlight that it is important to describe the incidence "per patient per year" to better describe the risk of ocular adverse events and to compare results between reports. As expected, the probability of RRD per patient increased with time and the number of injections in our study. However, we did not find any clinically significant increase in the probability of RRD with each successive injection, even after > 50 injections ($P = 0.95$). Thus, each successive injection without an RRD does not seem to increase the risk of developing an RRD at the next injection, which is reassuring. This finding supports an association rather than causation between IVI and RRD development.

Using a multivariate Cox proportional regression model, we found that older patients (HR [95% CI] = 1.81 [1.21−3.62] for every 10-year increase; $P < 0.01$) with worse presenting VA (HR [95% CI] = 0.85 [0.70−0.98] for every 10-letter score increase; $P = 0.02$) were associated

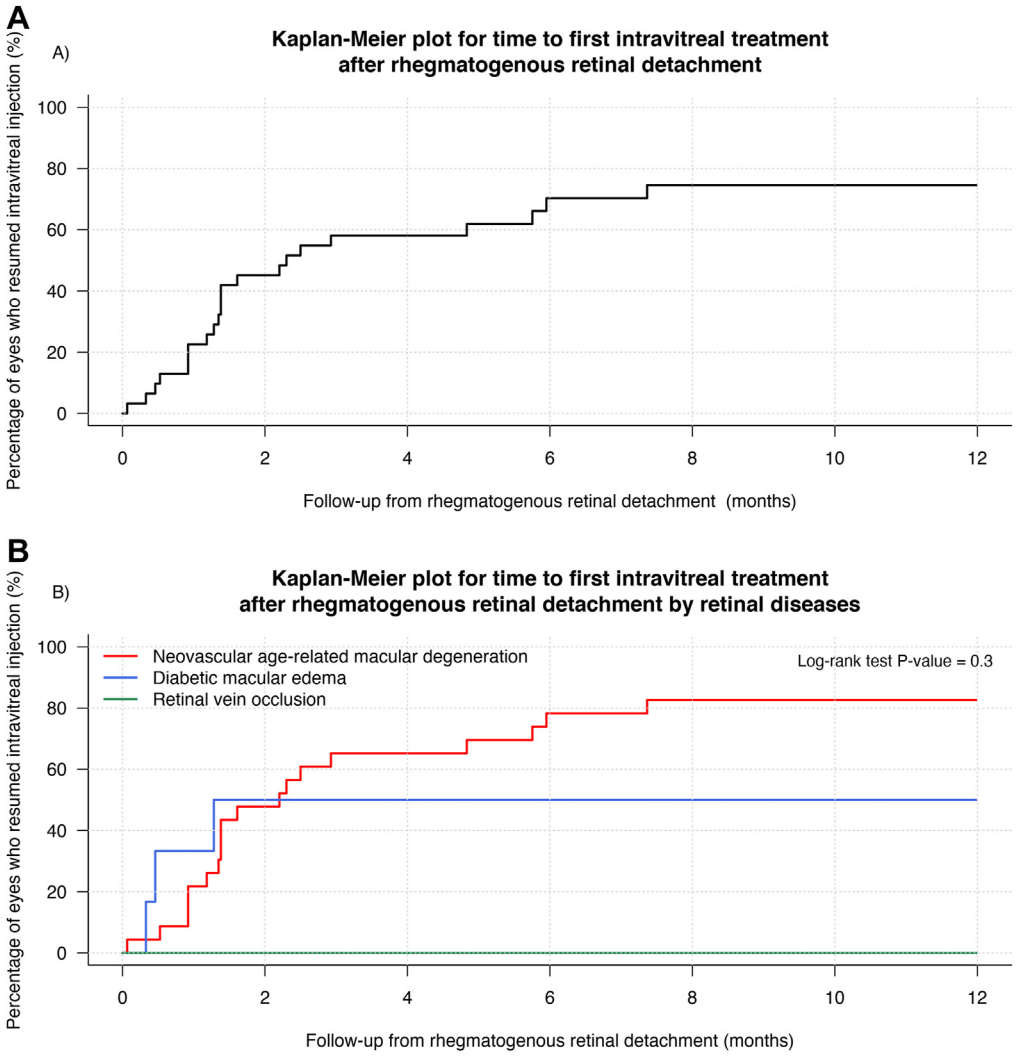

Figure 3. Kaplan–Meier plots for time to the first intravitreal injection after rhegmatogenous retinal detachment surgery in **A**, all cases and **B**, according to the type of retinal disease over 12 months.

with a greater risk of RRD development after IVT. This is consistent with the findings of the previous reports, especially population-based studies that showed that patients aged > 60 years were more at risk of RRD than younger patients.[13,21,22] Regarding presenting VA, patients with poor VA may find it more difficult to recognize a further decrease in VA or visual symptoms related to RRD. In addition, eyes with more advanced retinal disease may be more at risk of complications. We also studied whether lens status could influence the occurrence of RRD after IVT. A history of cataract surgery has been associated with the development of posterior vitreous detachment, which may increase vitreous traction on the retina and the risk of retinal tears and subsequent RRD.[23] However, lens status was not significantly associated with RRD development after IVT in our study. Of clinical interest, the type of retinal disease was not significantly associated with RRD development in our analysis, as reported in the previous studies.[12,24] Also, we did not observe that the type of VEGF inhibitor influenced the risk of development of RRD after IVT after adjustment for multiple comparisons.

Our findings highlight the poor visual outcomes of eyes developing RRD after IVT of VEGF inhibitors, with only one-third of the eyes with RRD recovering prior RRD VA at 12 months. The mean visual loss at 1 year from prior RRD was 15 letters (3 lines) in our study. Recently, a monocentric retrospective study found a mean visual loss at last observation (average follow-up of 19 months) from the baseline visit of 5 lines, with an increased average loss of 6 lines for macula-off RRD.[24] Unfortunately, our database did not collect the initial RRD characteristics, severity, and how it was managed, which did not allow us to compare the visual outcomes of eyes with RRD according to important functional and anatomical prognosis factors such as initial macula status or grade of proliferative vitreoretinopathy, for example. Nevertheless, our data highlight the severity of this rare complication in eyes with pre-existing macular disease at 1 year.

Table 4. Synthesis of the Literature

Name of the Study (type of VEGF inhibitors/retinal disease)	Rate of RRD per IVT (%)
Clinical trials	
The VISION trial[16] (pegaptanib/AMD)	1 per 1250 IVT (0.08%)
The minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of AMD trial (ranibizumab/AMD)[1]	1 per 8500 IVT (0.012%)
The RISE and RIDE trial (ranibizumab/DME)[9]	1 per 8223 IVT (0.012%)
The CATT trial (bevacizumab or ranibizumab/AMD)[17]	1 per 1833 IVT (0.054%)
The CRUISE trial (ranibizumab/RVO)[10]	0 per approximately 3500 IVT
The VIEW 1 trial (aflibercept and ranibizumab/AMD)[4]	1 per approximately 13000 IVT (0.008%)
Retrospective observational studies	
Meyer et al[18] (bevacizumab or ranibizumab/RVO, AMD, DME, retinal haemangioma, or Irvine-Gass syndrome)	1 per 7188 IVT (0.014%)
Storey et al[12] (aflibercept, bevacizumab or ranibizumab, AMD and RVO)	1 per 7532 IVT (0.013%)
Mammo et al[13] (not specified, AMD)	1 per 11 941 IVT (0.008%)
Registry-based study	
The Fight Retinal Blindness! registry (aflibercept, bevacizumab or ranibizumab/RVO, AMD, or DME)	1 per 7383 (0.014%)

AMD = age-related macular degeneration; CATT = comparison of age-related macular degeneration treatments trial; CRUISE = study of the efficacy and safety of ranibizumab injection in patients with macular edema secondary to central retinal vein occlusion; DME = diabetic macular edema; IVT = intravitreal injection; RISE and RIDE = ranibizumab for diabetic macular edema; RRD= rhegmatogenous retinal detachment; RVO = retinal vein occlusion; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF inhibition study in ocular neovascularization.

The median time to IVT resumption for macular disease in cases was approximately 2 months in our analysis, which is in agreement with that reported in the previous studies.[12,13] Furthermore, cases with RRD were given fewer IVTs over the year after the RRD than matched control eyes (3 vs. 6 IVT, $P = 0.02$), which has also been previously described.[13] The vitreous cavity is a reservoir for proinflammatory and angiogenic factors in the eye. Its disappearance after vitrectomy may explain the reduced need for IVT VEGF inhibitors.[25] Mammo et al[13] suggested that the increased oxygenation of the vitreous humor after vitrectomy reduces VEGF expression, thereby leading to less exudation and a decreased need for IVT after surgery. The decrease in the need for IVT after RRD was not related to a lack of follow-up as the median number of visits at 1 year in cases with RRD was not different from matched control eyes. However, we cannot conclude from our data because surgical procedure characteristics, such as surgical technique (vitrectomy or scleral buckle) or the type of tamponade agent used, were not collected in the database and could significantly influence the number of injections after RRD. In addition, many cases with RRD had poor vision postoperatively and may have been preferentially observed rather than treated despite any active exudation, given the visual prognosis.

The strengths of this study include the use of the Fight Retinal Blindness! registry that collected RRD diagnostic data for up to 14 years in routine clinical practice with > 16 000 tracked eyes that received collectively approximately 260 000 IVTs. An original finding of our study was to report both RRD incidence "per IVT" and "per patient per year" over a long period. Our study reported treatment and VA outcomes up to 12 months and were compared with matched controls, and we described the influence of RRD on the VEGF treatment course for various retinal diseases. Our data provides us with more data to better inform our treated patients regarding the risk and outcomes of RRD after IVT.

We acknowledge some weaknesses that were mostly inherent in the retrospective nature of the study. First, the estimated incidence may have been underestimated because cases were self-reported. Although variability exists in the quality of data in observational studies, the Fight Retinal Blindness! Registry system includes quality and verified measures that eliminate out-of-range and missing data.[14] Second, we acknowledge that the causality between IVI and development of RRD cannot be certain. We have collected data on all RRDs that developed 90 days after IVIs without any other ocular procedure in between. The postoperative period is usually considered to be 90 days, and similar published studies on IVI and RRD have used the same time interval definition.[12] Our analysis using an extensive database confirmed that even with a significant time interval of 90 days, the risk of RRD development after IVI remained extremely low, which is reassuring for clinical practice. This also supports an association rather than causation between IVI and RRD development. Third, pathologic myopia, a well-known risk factor of RRD,[8] has not been recorded in the Fight Retinal Blindness! AMD, RVO, and DME modules. We could not adjust our analysis on this factor, which might have impacted our results. Fourth, the number of cases with RRD was relatively low in our study as this complication is uncommon. However, our database study is one of the most extensive series of RRD after IVT, with a cohort of >16 000 tracked eyes that collectively received 260 000 IVT over 14 years. Fifth, our study included eyes with DME, with diabetic retinopathy treated with anti-VEGF agents that may develop retinal detachment related to tractional causes after IVT. We cannot exclude that some eyes with RRD have a tractional origin. However, we did not find an increased risk of developing RRD after IVT in eyes treated for DME. Thus, it is unlikely that tractional RRDs were included in this analysis. Lastly, we lacked information on the IVT procedure since the Fight Retinal Blindness!

database does not monitor individual practitioner techniques at each injection. However, IVT was performed following recommendations and guidelines and reflected routine clinical practice. Therefore, we were not able to assess the RRD risk associated with different IVT techniques.

To conclude, the estimated incidence and rate of RRD within 3 months after VEGF inhibitor IVT therapy were low and similar to those reported in other large-scale studies. Each successive injection without an RRD does not seem to increase the risk of developing an RRD at the next injection, which is also reassuring for clinical practice. Older patients with low presenting VA were at a greater risk of RRD after IVT. Overall, the 12-month visual outcomes were poor in these eyes with pre-existing macular disease.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Mater Private Hospital Institutional Review Board in Dublin, Ireland, the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, the Caldicott Guardian at the Royal Free London NHS Foundation Trust, the SingHealth Singapore, the Spanish Institutional Review Board (Comité Etico de Investigación Medica, Hospital Clínic de Barcelona, Spain) and the Cantonal Ethics Committee Zurich. Because of its noninterventional character, the approval of the use of the registry was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands. All patients gave consent. Informed consent ("opt-in consent") was sought from the patients in France, Ireland, Italy, Netherlands, Spain, Singapore, Switzerland and the United Kingdom. Ethics committees in Australia and New Zealand approved the use of "opt-out" patient consent. This study adhered to the tenets of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational studies in Epidemiology statements for reporting observational studies.

No animal subjects were used in this study.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CI** = confidence interval; **DME** = diabetic macular edema; **HR** = hazard ratio; **IVT** = intravitreal injection; **RRD** = rhegmatogenous retinal detachment; **RVO** = retinal vein occlusion; **VA** = visual acuity

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