

Ten-year real-world outcomes of antivasular endothelial growth factor therapy in neovascular age-related macular degeneration using pro re nata regimen

Pekko Hujanen,^{1,2} Heikki Ruha,^{1,2} Eemil Lehtonen,^{1,2} Inka Pirinen,^{1,2} Heini Huhtala,³ Anu Vaajanen,² Ulla Syvänen,¹ Anja Tuulonen,¹ Hannele Uusitalo-Järvinen ^{1,2}

To cite: Hujanen P, Ruha H, Lehtonen E, *et al*. Ten-year real-world outcomes of antivasular endothelial growth factor therapy in neovascular age-related macular degeneration using pro re nata regimen. *BMJ Open Ophthalmology* 2023;**8**:e001328. doi:10.1136/bmjophth-2023-001328

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjophth-2023-001328>).

Received 1 May 2023
Accepted 1 August 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Tays Eye Centre, Tampere University Hospital, Tampere, Finland

²Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

³Faculty of Social Sciences, Tampere University, Tampere, Finland

Correspondence to

Dr Hannele Uusitalo-Järvinen; hannele.uusitalo-jarvinen@pirha.fi

ABSTRACT

Background/aims To analyse long-term outcomes of antivasular endothelial growth factor (anti-VEGF) therapy for the treatment of neovascular age-related macular degeneration (nAMD) using pro re nata (PRN) regimen in a single-centre clinical practice.

Methods All patients receiving intravitreal injection (IVI) for nAMD between 1 January 2008 and 31 December 2020 were searched from electronic medical records. All 3844 treatment-naïve eyes of 3008 patients were included with a total of 50 146 IVIs (87% bevacizumab) administered. Main outcome measures were mean change in visual acuity (VA) from baseline, proportion of eyes within 15 letters of baseline, proportion of eyes with VA $\geq 20/40$ Snellen and $\leq 20/200$ Snellen, number of annual visits and number of annual IVIs.

Results The mean baseline VA was 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and the mean change in VA from baseline was +2, +2, ± 0 , -2, -2 and -4 ETDRS letters at year 1, 2, 3, 5, 7 and 10, respectively. Proportions of eyes within 15 letters of baseline were 88%, 87%, 82%, 80%, 76% and 72% at the end of years 1, 2, 3, 5, 7 and 10, respectively. The median number of annual IVI was 6 at years 1–7 and 5 at year 10. The median number of annual total visits was 10 at year 1, 9 at years 2–7 and 8 at year 10, respectively.

Conclusions VA was maintained short-term and long-term with anti-VEGF therapy using PRN treatment regimen.

INTRODUCTION

The efficacy of antivasular endothelial growth factors (anti-VEGFs) in neovascular age-related macular degeneration (nAMD) has been clearly demonstrated in randomised clinical trials (RCTs).^{1 2} In the pivotal RCTs, fixed monthly ranibizumab and bevacizumab injections, as well as fixed bimonthly aflibercept (after the first 3 monthly injections) resulted in visual acuity (VA) gain of 6–11 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 2 years.^{3–6}

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Short-term efficacy of antivasular endothelial growth factor (anti-VEGF) therapy in neovascular age-related macular degeneration (nAMD) using fixed, pro re nata (PRN) and Treat and Extend regimens has been clearly demonstrated in several randomised clinical trials. However, long-term outcomes of anti-VEGF therapy have been scarcely reported.

WHAT THIS STUDY ADDS

⇒ This study evaluates 10-year outcomes of anti-VEGF therapy for nAMD using PRN treatment regimen in real-world clinical practice. The study demonstrates that visual acuity was maintained up to 10 years with a median of 6 annual intravitreal injections and 3–4 annual non-injection visits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The present study demonstrates that visual acuity can be maintained long-term with anti-VEGF therapy using PRN treatment regimen in real-world clinical practice.

In real-world, the fixed treatment regimens cause a substantial burden on patients and caregivers and may also lead to unnecessary treatments. To overcome these challenges, more flexible regimens such as pro re nata (PRN) and treat-and-extend (T&E) have been developed. Generally, the aim of the PRN regimen is to decrease the number of potentially unnecessary injections, whereas T&E regimen aims to decrease the number of potentially unnecessary clinic visits. However, both PRN and T&E regimens have their own shortcomings. PRN regimen requires monthly visits while T&E may lead to unnecessary injections and become complicated to implement in case of bilateral nAMD.



A Cochrane review including 15 RCTs and investigating the effects of fixed monthly, PRN and T&E treatment regimens in newly diagnosed nAMD showed +8 letters mean change in VA in fixed monthly regimen at 1 year.² Compared with fixed monthly regimen, the mean difference in VA change for the standard PRN regimen was -1.7 letters favouring monthly injections, and the mean difference in VA change for T&E regimen was +0.5 letters. Since the Cochrane review, the first and only RCT to date, comparing directly the efficacy of T&E and PRN regimens for nAMD was released.⁷ This RCT found that T&E ranibizumab were non-inferior to PRN in treatment naïve nAMD at 12 months (+6.4 vs +8.0 letters in T&E vs PRN arms, respectively).⁷

Regardless of treatment regimen, the challenge lies in the applicability of RCT outcomes in real-life settings. The outcomes in ideal and selected RCT settings differ from the outcomes in real-world practices which include more diverse patients with extensive comorbidities compared with the tight and selected RCT samples. Real-world data (RWD) are required for the assessment of everyday effectiveness of anti-VEGF therapy. In addition, RWD provide an opportunity to assess long-term outcomes compared with relatively short-term RCTs and when comparing outcomes between volume-based fee for-service systems and value-based systems.⁸

The present study describes 10-year outcomes of nAMD treated eyes with anti-VEGF intravitreal injections (IVIs) in routine clinical practice using PRN treatment regimen.

MATERIALS AND METHODS

This is a single-centre, retrospective study conducted in Tays Eye Centre, Tampere University Hospital, Finland, which is responsible for organising all public eye care services for 500 000 inhabitants living in Pirkanmaa Well-being Service County. The study was approved by the Tays Research Services (number R21519/2021) and was conducted in accordance with the Declaration of Helsinki. As patient identifiers were removed completely after the data collection, the ethics committee of Pirkanmaa Hospital District determined that formal ethics approval was not required. Patients or the public were not involved in the design, or conduct, or reporting of our research.

The anti-VEGF treatment protocol followed a PRN regimen initiating treatment with a loading dose of 3 monthly anti-VEGF IVIs, after which the outcome was assessed. In case of inadequate therapeutic response or disease reactivation, treatment was continued with cycles of three injections. The treatment criterion was VA \geq 0.1 and active disease. Patients were discharged to home monitoring after inactive disease period of 6–12 months. Nevertheless, treating ophthalmologists were allowed to deviate from the protocol based on their own clinical judgement.

Over the follow-up years 2008–2020, the treatment protocol underwent several changes. First, injection and/or monitoring visits occurred every 6–8 weeks until November 2011, and then every 4–6 weeks thereafter.

Second, the majority of IVIs were administered by nurses instead of physicians starting in 2010. Third, bevacizumab was introduced in 2009 and was the most used anti-VEGF agent from 2009 to 2020. Finally, aflibercept was introduced in 2014 and the practise of dividing aflibercept vial into three pre-filled syringes initiated in 2016, allowing for a greater number of injections at a lower cost.⁹

The electronic medical records (EMRs) of Tays Eye Centre were searched for all patients with an ICD-10 code for nAMD (H35.31 in International Classification of Diseases, 10th revision) and \geq 1 code for intravitreal injection (CKD05) between 1 January 2008 and 31 December 2020. The study was restricted to treatment-naïve eyes. Exclusion criteria were treatment initiation before 2008, anti-VEGF injection for other reasons than nAMD, and use of laser photocoagulation, photodynamic therapy or intravitreal steroids. Eyes without baseline VA were excluded from visual outcome analysis. Eyes that started treatment in 2020 were excluded from 1-year lost to follow-up analysis, and eyes that started treatment in 2019–2020 were excluded from 2-year lost to follow-up analysis. Corresponding exclusions were applied to the 3, 5, 7 and 10-year lost to follow-up analyses.

Data collected from EMR included age, gender, VA at the time of diagnosis and during follow-up visits, dates of IVIs and monitoring visits, the anti-VEGF compound used and date of death. The data were collected from the date of nAMD diagnosis until the end of treatment and/or monitoring, or until 31 December 2020. VA was measured using Snellen chart and refraction, habitual correction, pinhole or a combination, or by using Nidek AR-360A autorefractometer (Nidek Co., LTD, Gama-gori, Aichi, Japan) since 2011. Snellen VA was converted into ETDRS letters using the formula $85+50*\log(\text{Snellen fraction})$.¹⁰ Very low VA measurements were analysed by substituting counting fingers with 3 ETDRS letters, hand movements with two letters and light perception with one letter.¹¹

If both eyes were diagnosed with nAMD on the same day, the eye labelled as the first eye and the second eye were randomly selected. The data were manually collected and meticulously checked for manual input errors during the data analysis period. In addition, a systematic screening for input errors and missing data was executed before statistical analysis. All eyes, the first and second treated eyes were analysed separately to describe data as comprehensively as possible without leaving anything out (online supplemental tables 1–4).

In accordance with the International Consortium for Health Outcomes Measurement (ICHOM) recommendations,¹² the outcome measures included the mean change in VA from baseline, proportion of eyes gaining \geq 5 letters, and proportion of eyes with stable vision (within 15 letters of baseline), VA \geq 20/40 Snellen and VA \leq 20/200 Snellen. Furthermore, outcome measures included baseline characteristics such as age, gender and mean baseline VA, as well as the number of annual visits and the number of annual IVIs for each treatment year.

Table 1 Baseline characteristics of patients and eyes

	Baseline	Patients and eyes with completed follow-up years					
		1	2	3	5	7	10
Patients, n	3008	1964	1219	797	349	158	33
Age, years							
Median	80	79	79	78	77	77	77
IQR	74–85	74–84	73–84	73–83	72–81	72–81	73–81
Range	50–101	52–101	52–97	54–97	54–93	56–92	60–92
Females, n	2032	1342	822	543	240	111	23
%	68	68	67	68	69	70	70
All eyes, n	3844	2553	1615	1055	469	194	43
Baseline VA, mean	55	59	61	62	63	62	61
SD	20	17	16	16	14	16	16
Eyes with VA ≤35 ETDRS letters, n	452	142	66	40	11	7	2
%	12	6	4	4	2	4	5
Eyes with VA ≥70 ETDRS letters,† n	744	773	403	281	133	56	12
%	20	22	25	27	28	29	28

*Snellen equivalent ≤20/200 Snellen.
 †Snellen equivalent ≥20/40 Snellen.
 ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

The study also recorded the rate of second eye involvement, the rates and reasons for ending treatment, as well as losses of follow-up and the number of different anti-VEGF compounds used.

All statistical analyses were conducted using SPSS V.27 (IBM Corp., Armonk, New York, USA). One-way analysis of covariance (ANCOVA) was conducted with VA change as the dependent variable and 10 or more IVIs in the first treatment year group (0/1) as the independent variable. Baseline VA was included as a covariate in the analysis to account for its potential influence on VA change. A *p* value of ≤0.05 was considered statistically significant.

Snellen VA values were converted into ETDRS letters and treated as a continuous variable. To account for missing VA data, Last-Observation-Carried-Forward (LOCF) analysis was used (online supplemental table 6). When VA data were not available at the time of decision for treatment, the baseline VA was imputed from a prior visit within 1 month.

RESULTS

The study included 3844 eyes of 3008 patients with nAMD, of whom 836 (28%) had second eye involvement during the study period. Baseline demographics are summarised in table 1 for all treated eyes and in online supplemental table 1 for the first and second treated eyes. The overall median baseline age for all treated eyes was 80 years with 69% female patients. Sixty-four eyes (1.7%) had unknown baseline VA and were excluded from VA outcome analysis. The remaining 3780 eyes had mean

baseline VA (SD) of 55 (±20) letters for all treated eyes, 54 (±21) letters for the first and 59 (±19) letters for the second eye involved (online supplemental table 1). The mean baseline VA was higher for those who continued treatment for more than 1 year (table 1, online supplemental tables 1 and 2).

Of 50 146 IVIs administered, bevacizumab was used in 43 394 (87%), ranibizumab in 813 (2%) and aflibercept in 5850 (12%) injections.

Changes of VA from baseline at 1, 2, 3, 5, 7 and 10 years were analysed for eyes that completed respective follow-up time. The mean increase in VA from baseline was +2 letter at year 1, where after it gradually declined to the baseline level at year 3 and to –4 letters at year 10 (figure 1A). The mean change of VA from baseline was slightly better in the first treated eye compared with the second treated eye (online supplemental table 2).

To study the role of baseline VA on visual outcomes, mean change in VA was evaluated in subgroups of eyes with baseline VA of ≤35, 36–59, 60–69 and ≥70 ETDRS letters. The largest benefit was seen in patients with low baseline VAs (figure 1B).

The proportion of eyes with good baseline VA (VA ≥70 ETDRS letters) increased at year 1 following a gradual decline to baseline level at year 10. Proportion of eyes with poor VA (VA ≤35 ETDRS letters) decreased from baseline to year 1 and remained at the same level up to 7 years where after it increased back to the baseline level by year 10 (figure 1B).

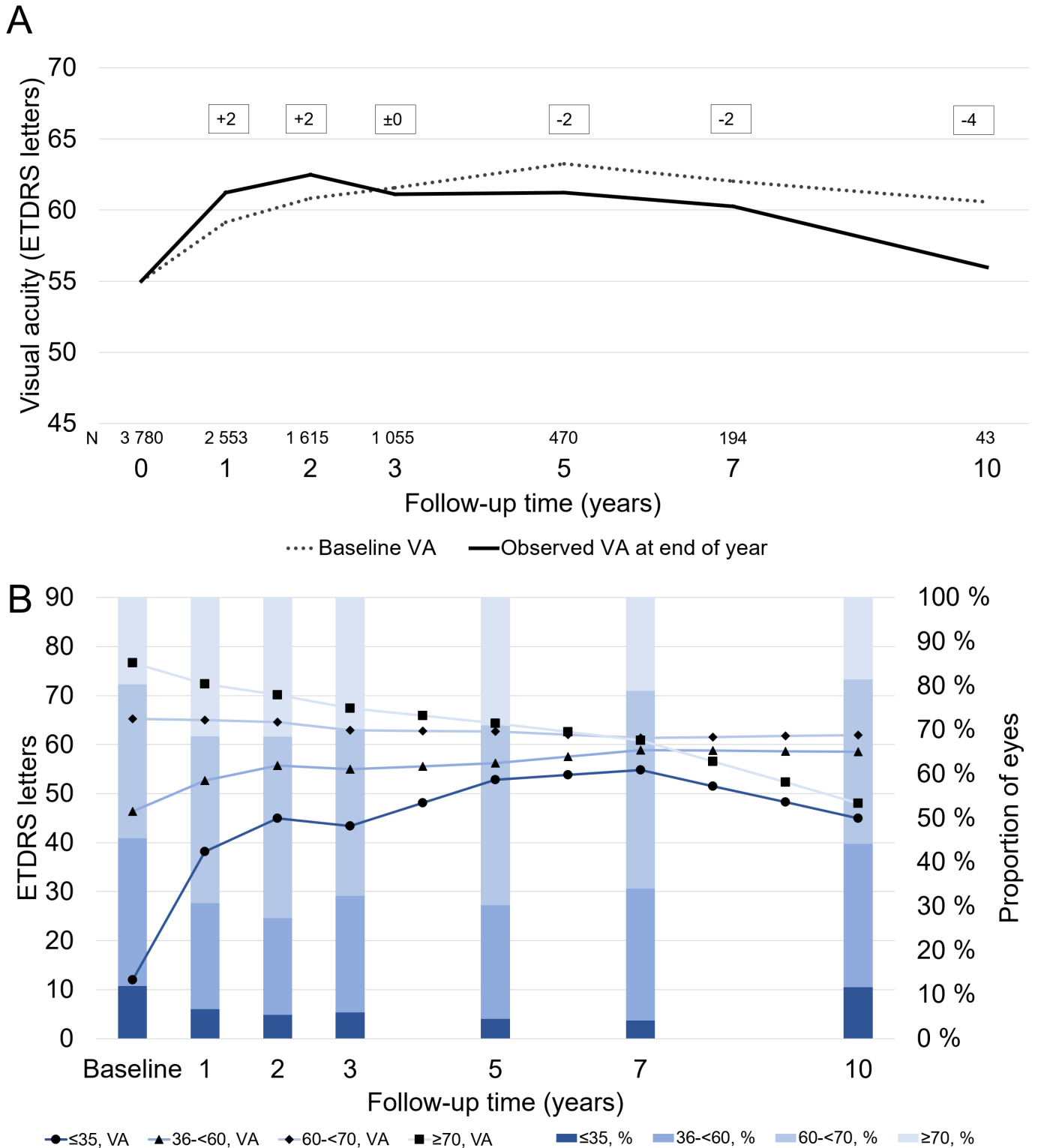


Figure 1 Change in visual acuity from baseline in patients with nAMD treated with anti-VEGF therapy. The graphs shows visual acuity at 1, 2, 3, 5, 7 and 10 years (solid line) after the anti-VEGF treatment was started (A). The baseline visual acuity (dotted line) is shown in each follow-up point for eyes which completed the respective follow-up time. Change in acuity in ETDRS letters is boxed above the lines and number of eyes is reported below the x-axis (A). Change in visual acuity stratified by baseline visual acuity and proportion of eyes with VA ≤35, 36–60, 60–70 and ≥70 ETDRS letters at years 1, 2, 3, 5, 7 and 10 (B). Anti-VEGF, anti-vascular endothelial growth factor; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; VA, visual acuity.

Table 2 Eyes with stable vision (visual loss >15 letters) and gain of ≥5 letters

	Patients and eyes with completed follow-up years					
	1	2	3	5	7	10
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Eyes with stable vision	2243 (88)	1402 (87)	866 (82)	377 (80)	148 (76)	31(72)
Eyes gaining ≥5 letters	967 (38)	610 (38)	362 (34)	152 (32)	69 (36)	16 (37)
Eyes total	2553	1615	1055	470	194	43

Proportion of eyes gaining ≥5 letters and eyes with stable vision (within 15 letters of baseline) at 1, 2, 3, 5, 7 and 10 years were analysed for eyes that completed respective follow-up time. Results are illustrated in [table 2](#).

We also analysed visual outcomes in a subgroup of eyes with ≥10 annual IVIs at treatment year 1 (n=62). In this subgroup, the mean change in VA appeared to be better: +6, +7, +7, +8 and +1 letters at years 1, 2, 3, 5 and 7 compared with +2, +2, ±0, -2 and -2 in all eyes respectively. The baseline VA for the eyes completing 1-year, 2-year, 3-year, 5-year and 7-year follow-up and receiving ≥10 injections during first treatment year was 57 (n=62), 58 (n=45), 57 (n=31), 56 (n=17) and 56 (n=9 eyes) whereas baseline for all eyes completing 1-year, 2-year, 3-year, 5-year and 7-year follow-up was 59, 61, 62, 63 and 62. After adjusting the effect of baseline VA, the change in mean VA at year 1, 2, 3, 5 and 7 was not statistically significant between the eyes receiving ≥10 IVIs compared with eyes receiving <10 IVIs during the first treatment year using one-way ANCOVA (F 0.01–3.35 [df 1], p=0.07–0.92).

The number of annual intravitreal anti-VEGF injections and non-injection visits at 1, 2, 3, 5, 7 and 10 years are described in [table 3](#). There was a shift towards higher frequency of treatments during the study period as the median annual number of IVIs administered during the first year increased gradually from 5 in 2008 to 7 in 2017–2019 and the frequency annual of non-injection visits during first treatment year increased from 3 in 2008–2011

to 4 in 2012–2019, respectively (online supplemental tables 3 and 4).

To find out if higher number of injections leads to a better VA outcome during long-term treatment, we decided to compare our outcomes to other studies with 7-year and 10-year follow-up.^{13–19} Mean cumulative number of injections, baseline VA, final VA and change in VA from baseline with Pearson correlates are shown in [table 4](#). A positive correlation with cumulative number of injections and VA change from baseline as well as final VA was observed. Although correlation appeared to be clear, especially with 10-year follow-up studies, no statistical significance was observed (p=0.14–0.97, two-tail sig.).

Percentages of eyes lost to follow-up were 26%, 47%, 61%, 76%, 86% and 92% by the treatment years 1, 2, 3, 5, 7 and 10, respectively (online supplemental tables 1–5). Total of 2559 eyes were lost to follow-up, of which 1121 eyes (44%) due to poor treatment result, 662 eyes (26%) due to inactivation of disease, 251 eyes (10%) due to poor general health, 221 eyes (9%) due to other or unknown reason, 187 eyes (7%) due to patient declined treatment and 117 eyes (5%) due to patient death within 1 month of last visit.

DISCUSSION

This retrospective study including all IVI treated eyes in Tays Eye Centre in 2008–2020 shows that the anti-VEGF treatment for nAMD using PRN regimen and mostly

Table 3 Median number (MD) of annual and mean number of cumulative intravitreal anti-VEGF injections and non-injection visits stratified by year completed

	Patients and eyes with completed follow-up years					
	1	2	3	5	7	10
	MD (IQR)	MD (IQR)	MD (IQR)	MD (IQR)	MD (IQR)	MD (IQR)
Intravitreal injections/year	6 (5–8)	6 (3–7)	6 (3–7)	6 (4–7)	6 (3–7)	5 (2–7)
Visits/year	4 (3–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Cumulative IVI count	6.2 (2.1)	12 (4.1)	17 (5.7)	28 (8.9)	39 (12)	54 (17)
Cumulative visit count†	3.8 (1.2)	7.0 (2.0)	10 (2.6)	16 (3.9)	22 (4.8)	29 (5.6)

*At the end of each year.

†Non-injection visit.

anti-VEGF, antivascular endothelial growth factor; IVI, intravitreal injection.



Table 4 Real-world studies with 7-year or 10-year follow-up with correlation of mean number of total injections given, baseline visual acuity, final visual acuity and change in visual acuity

	Baseline VA (ETDRS letters, mean)	Mean change in VA (ETDRS letters, mean)	Mean total number of injections	Final VA (ETDRS letters, mean)
Studies with 7-year follow-up				
This study, 7-year follow-up (n=194)	62	-1.8	38.9	60.2
Rofagha <i>et al</i> ¹³ SEVEN-UP (n=65)	54.3	-8.6	34.6	45.7
Gillies <i>et al</i> ¹⁴ (n=131)	61	-2.7	36	58.3
Berg <i>et al</i> ¹⁵ (n=40)	62.6	-0.9	45	61.7
Westborg <i>et al</i> ¹⁶ (n=322)	54.3	-1	21.4	53.3
Brynskov <i>et al</i> ¹⁷ (n=288)	63	-3.3	30.9	59.7
Pearson correlate		0.18†	0.43*	
P value (two-tail sig.)		0.97	0.40	
Studies with 10-year follow-up				
This study, 10-year follow-up (n=43)	61	-4.3	53.8	56.7
Gillies <i>et al</i> ¹⁸ 2019 ANZ (n=132)	60.7	-0.9	53	59.8
Gillies <i>et al</i> 2019 SWI (n=37)	61.6	-14.9	42	46.7
Chandra <i>et al</i> ¹⁹ (n=149)	59.5	-2.1	52.2	57.4
Brynskov <i>et al</i> ¹⁷ (n=74)	61.5	-5	42.9	56.5
Pearson correlate		0.76*	0.72†	
P value (two-tail sig.)		0.14	0.17	

*Pearson correlation of mean change in VA and mean total number of injections.
†Pearson correlation of final VA and mean total number of injections.
ANZ, New Zealand; ETDRS, Early Treatment Diabetic Retinopathy Study; SWI, Switzerland; VA, visual acuity.

bevacizumab (87%) stabilised VA for 10 years in real-life setting in patients not lost to follow-up.

Although VA was maintained, the initial gain in VA observed in our study was lower than that reported in clinical trials with fixed monthly treatment and/or monitoring.^{11 20} However, the short-term visual outcome was in accordance with several previous real-life studies with similar number of yearly IVIs at year 1^{16 20–26} and at year 2.^{26–28} Real-world studies with higher total injection count at year 1 (≥ 7 injections)^{23 29} and year 2 (≥ 13 injections)^{23 30 31} have yielded slightly higher visual gains. However, not only the injection frequency but also the baseline characteristics of study population may affect the VA outcomes. In the studies with higher injection frequency, the baseline VA was lower compared with our study, which may have contributed to larger VA gains.

In our study, there was no statistically significant difference in VA gain between the eyes that received ≥ 10 IVI and those that received < 10 IVI during the first treatment year after adjusting for the effect of baseline VA. This may suggest that some eyes gain VA with less frequent injections while some eyes need more frequent injections. Using PRN treatment regimen with frequent visits it is possible to find the eyes which need more frequent injections. This is in accordance with other studies, where PRN was non-inferior compared with fixed treatment regimen.²

The baseline VA is known to correlate negatively with the gains in VA due to ceiling effect which has been

shown in several previous analyses.^{14 21 23 25 32} To address this issue, the ICHOM working group suggested evaluating the proportion of eyes with stable, poor and good vision. The LUMINOUS study²² reported that 89% of eyes retained stable vision (< 15 letter visual loss from baseline) at year 1 using ranibizumab, while Liew *et al*²¹ reported that 91% of eyes retained stable vision at year 1. Arnold *et al*³⁰ reported that 91% of eyes avoided ≥ 15 letter vision loss at year 2. These findings are consistent with our study, which found that 88% and 87% of eyes retained stable vision at years 1 and 2, respectively. Furthermore, Arnold *et al*³⁰ reported that the proportion of eyes with good VA (VA $\geq 20/40$ Snellen) increased from 27% at baseline to 45% at year 2 and the proportion of eyes with poor VA (VA $\leq 20/200$ Snellen) decreased from 13% at baseline to 11% at year 2. In contrast to these results, we found an increase in proportion of good VA from 25% at baseline to 32% at year 2 and an increase in the proportion of eyes with poor VA from 4% at baseline to 5% at year 2.

The use of proportions of eyes with stable, poor or good vision as a benchmark has certain limitations. First, there may be substantial variations in treatment protocols, resulting in skewed distributions of eyes with good and poor VA at baseline. For instance, the inclusion criteria for treatment may be more stringent in some clinics, leading to a lower proportion of eyes with poor VA at baseline, as is the case in our study. Second, the loss of eyes to follow-up may drastically skew the distribution;

for example, if eyes with the worst VA are released from routine check-ups, the distribution may be skewed towards eyes with better vision. The ICHOM criteria do not provide recommendations on how to statistically manage the effect of lost eyes when benchmarking visual outcomes.

No long-term RCT data are available for treatment outcomes with ≥ 5 years of follow-up. However, several real-world studies with long follow-up time have been published recently. Gillies *et al*⁴ reported +0.7 letter change from baseline VA of 60 letters, Chandra *et al*³³ reported -2.9 letter change from baseline VA of 58 letters with mean of 24 injections and Zhu *et al*³⁴ reported -2.4 letter change from baseline VA of 54 letters with mean of 31 injections at year 5. These findings are similar to ours with -2 letter change from baseline VA of 63 letters with mean of 28 injections at year 5.

A recent review of 5-year nAMD treatment outcomes showed a positive correlation between number of injections administered and VA change from baseline.³⁵ When we analysed outcomes from our study and other 7-year and 10-year follow-up studies, we also found a positive correlation between cumulative number of injections and final VA and change in VA from baseline, although this finding did not reach statistical significance due to small number of studies with ≥ 7 -year follow-up. There were two 10-year studies, with similar number injection (42.9 vs 42) and baseline VA (61.5 vs 61.6), but significantly different outcomes (-5 letters vs -14.9 letters). The study with more consistent injection rate with mean of 5.4 injections in the first year followed by 4.0–4.3 injections/year demonstrated better VA outcome compared with study with median of 6 injections in the first year followed by 2–3 injection/year in years 2–7 and 3–5 injection/year in years 8–10. This indicates that VA is maintained more likely if injections are given evenly.

Drop-out percentage was high in our study as observed in other real-world studies. There is no clear consensus how to address missing data especially when comparing interventions.¹¹ Treatment outcomes may be skewed if complete case analysis is used and patients who do better are enriched in analysis when patients with poor treatment result are removed from data. Differences in treatment protocols between clinics may explain differences in drop-out rates reported in real-world studies, for example, treatment and patient observation can carry on longer with poor VA in some clinics, whereas treatment would be stopped in other clinics with same VA and patient is thus lost to follow-up. Protocols also differ in how long patients are observed after inactivation of disease.

The strength of this real-world study is to transparently expose all our long-term outcomes of nAMD treatments to be compared with other RWD sets. Since Tays Eye Centre is the only clinic providing nAMD treatment for population living in hospital serving area, the study population is highly non-selected in terms of comorbidities, age and socioeconomic status, and represent mainly Caucasian

population. Treatment protocol has remained PRN over the follow-up time. It is extremely important to clearly report the number and reasons of dropouts to enable and promote comparisons of all outcomes between units and countries. Therefore, the baseline features of 1-year, 2-year, 3-year, 5-year, 7-year and 10-year completers were described separately. The data were manually collected and rigorously checked for input errors to make data as robust as possible.

Limitations of this report are related to the nature of any real-world settings like high drop-out rates and selection bias of patients with longer follow-up time which are obviously related to the high median age (80 years) of the treated patients. There were only 43 eyes with the 10-year follow-up (8% of those able to complete this follow-up), which may affect the generalisability of the 10-year VA outcomes. VA at end of observed year was generated using LOCF method and therefore observations may slightly overestimate VA since the trend of VA is generally declining over time. Not all baseline patient characteristics recommended by ICHOM working group were collected to enable assessment of baseline risk factors such as smoking status, VA in both eyes, type of macular degeneration, presence of geographic atrophy, subretinal fibrosis or pigment epithelial detachment and ocular comorbidities.

Overall, VA gains were most beneficial in eyes with lower baseline VA and mean VA was maintained long-term with PRN regimen if patient adherence was sufficient. Further investigation is needed to define optimal real-world treatment regimen which is personalised to patient baseline characteristics. Additionally, there is a need to address and develop statistical methods to analyse RWD as well as reporting protocols to promote (inter)national comparability of outcomes, especially with increase of continuous structured data collection using electronic health records.^{8 36}

Acknowledgements The authors would like to thank the Clinical Informatics Unit at the Tampere University Hospital for data curating, visualisation and analysis.

Contributors PH, HU-J and AT designed the research. PH, IP, HR and US performed the data collection. PH, HR, HH, AV, US, AT and HU-J analysed the data. PH, AT and HU-J wrote the manuscript. PH made the figures and tables. PH, IP, HH, US, AV, AT and HU-J reviewed the paper. HUJ is responsible for the overall content.

Funding The study was supported by the Competitive Research Funding of the Pirkanmaa Hospital District for AV (grant nos. R18502 and 9X060), AT (grant no. 9AA076), PH and HU-J (grant nos. MJ006H, MK343 and MK270), Finnish Eye Foundation for PH, AV and HU-J, LUX—foundation for glaucoma research (AV), Eemil Aaltonen Foundation and Finnish Ophthalmologist Association for PH.

Competing interests PH has received advisory board honorarium from Novartis and congress travel fees from Abbvie. HR: none to disclose. EL: none to disclose. IP: none to disclose. AV: none to disclose. US: none to disclose. HH: none to disclose. AT: Business Finland (directed by Finnish Ministry of Employment and Economy) supports the Public Innovative Procurement process for developing the package of the digital tools tailored to the needs of all five Finnish University eye clinics for collecting real-world data. Business Finland does not influence the contents of the procurement process nor the medical contents of the concept. AT has received no honorariums, payments nor any other form of direct personal support from industry. HU-J is an advisory board member for Abbvie, Bayer, Novartis and Roche and she has received lecture fees from Santen and Thea.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Hannele Uusitalo-Järvinen <http://orcid.org/0000-0002-2030-295X>

REFERENCES

- Solomon SD, Lindsley K, Vedula SS, *et al*. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2019;3:CD005139.
- Li E, Donati S, Lindsley KB, *et al*. Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2020;5:CD012208.
- Rosenfeld PJ, Brown DM, Heier JS, *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.
- Brown DM, Kaiser PK, Michels M, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–44.
- Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, *et al*. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results. *Ophthalmology* 2012;119:1388–98.
- Heier JS, Brown DM, Chong V, *et al*. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537–48.
- López Gálvez MI, Arias Barquet L, S Figueroa M, *et al*. Bimonthly, treat-and-extend and as-needed ranibizumab in naïve neovascular age-related macular degeneration patients: 12-month outcomes of a randomized study. *Acta Ophthalmol* 2020;98:e820–9.
- Tuulonen A, Kataja M, Aaltonen V, *et al*. A comprehensive model for measuring real-life cost-effectiveness in Eyecare: automation in care and evaluation of system ((aces-Rwm)TM). *Acta Ophthalmol* 2022;100:e833–40.
- Hujanen P, Tuulonen A, Uusitalo-Järvinen H. Real-world efficacy and safety of dividing aflibercept into three syringes in the treatment of wet age-related macular degeneration. *Acta Ophthalmol* 2019;97:e812–3.
- Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina* 2010;30:1046–50.
- Mehta H, Tufail A, Daien V, *et al*. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. *Prog Retin Eye Res* 2018;65:127–46.
- Rodrigues IA, Sprinkhuizen SM, Barthelmes D, *et al*. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. *Am J Ophthalmol* 2016;168:1–12.
- Rofagha S, Bhisitkul RB, Boyer DS, *et al*. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology* 2013;120:2292–9.
- Gillies MC, Campaign A, Barthelmes D, *et al*. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology* 2015;122:1837–45.
- Berg K, Roald AB, Navaratnam J, *et al*. An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration. *Acta Ophthalmol* 2017;95:796–802.
- Westborg I, Granstam E, Rosso A, *et al*. Treatment for neovascular age-related macular degeneration in Sweden: outcomes at seven years in the Swedish Macula register. *Acta Ophthalmol* 2017;95:787–95.
- Brynskov T, Munch IC, Larsen TM, *et al*. Real-world 10-year experiences with intravitreal treatment with ranibizumab and aflibercept for neovascular age-related macular degeneration. *Acta Ophthalmol* 2020;98:132–8.
- Gillies M, Arnold J, Bhandari S, *et al*. Ten-year treatment outcomes of neovascular age-related macular degeneration from two regions. *Am J Ophthalmol* 2020;210:116–24.
- Chandra S, Arpa C, Menon D, *et al*. Ten-year outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration. *Eye (Lond)* 2020;34:1888–96.
- Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. *Eye (Lond)* 2016;30:1526.
- On behalf of UK AMD EMR Users Group, Liew G, Lee AY, *et al*. The UK neovascular AMD database report 3: inter-centre variation in visual acuity outcomes and establishing real-world measures of care. *Eye* 2016;30:1462–8.
- Holz FG, Figueroa MS, Bandello F, *et al*. Ranibizumab treatment in treatment-naïve neovascular age-related macular degeneration. *Retina* 2020;40:1673–85.
- Fasler K, Moraes G, Wagner S, *et al*. One- and two-year visual outcomes from the Moorfields age-related macular degeneration database: a retrospective cohort study and an open science resource. *BMJ Open* 2019;9:e027441.
- Kiss S, Campbell J, Almony A, *et al*. Management and outcomes for neovascular age-related macular degeneration: analysis of United States electronic health records. *Ophthalmology* 2020;127:1179–88.
- Lee AY, Lee CS, Egan CA, *et al*. UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice. *Br J Ophthalmol* 2017;101:1683–8.
- Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology* 2014;121:1092–101.
- Kim LN, Mehta H, Barthelmes D, *et al*. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* 2016;36:1418–31.
- Holz FG, Tadayoni R, Beatty S, *et al*. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol* 2015;99:220–6.
- Talks JS, Lotery AJ, Ghanchi F, *et al*. First-year visual acuity outcomes of providing aflibercept according to the VIEW study protocol for age-related macular degeneration. *Ophthalmology* 2016;123:337–43.
- Arnold JJ, Campaign A, Barthelmes D, *et al*. Two-year outcomes of “treat and extend” intravitreal therapy for neovascular age-related macular degeneration. *Ophthalmology* 2015;122:1212–9.
- Barthelmes D, Nguyen V, Daien V, *et al*. Two year outcomes of ‘treat and extend’ intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. *Retina* 2018;38:20–8.
- Holz FG, Tadayoni R, Beatty S, *et al*. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br J Ophthalmol* 2016;100:1623–8.
- Chandra S, Rasheed R, Menon D, *et al*. Impact of injection frequency on 5-year real-world visual acuity outcomes of aflibercept therapy for neovascular age-related macular degeneration. *Eye* 2021;35:409–17.
- Zhu M, Chew JK, Broadhead GK, *et al*. Intravitreal ranibizumab for neovascular age-related macular degeneration in clinical practice: five-year treatment outcomes. *Graefes Arch Clin Exp Ophthalmol* 2015;253:1217–25.
- Qin VL, Young J, Silva FQ, *et al*. Outcomes of patients with exudative age-related macular degeneration treated with anti-vascular endothelial growth factor therapy for three or more years: a review of current outcomes. *Retina* 2018;38:1500–8.
- Kotecha D, Asselbergs FW, Achenbach S, *et al*. CODE-EHR best-practice framework for the use of structured electronic health-care records in clinical research. *Lancet Digit Health* 2022;4:e757–64.

Supplementary table 1. Baseline characteristics, first and second eyes.							
		Year completer					
	Baseline	1	2	3	5	7	10
First eyes	3 008	1 964	1 219	797	349	158	33
Age							
-Median	80	79	79	78	77	77	77
-IQR	74–85	74–84	73–83	73–83	73–82	73–82	73–81
-Range	50–101	52–101	52–97	54–97	54–93	56–92	60–92
Females	2 032	1 342	822	543	240	111	23
-%	68	68	67	68	69	70	70
Baseline VA, mean	54	58	60	60	62	61	60
-SD	21	17	16	16	14	16	14
Eyes with VA ≤35 ETDRS letters *, n	381	121	57	35	9	6	1
-%	13	6	5	4	3	4	8
Eyes with VA ≥70 ETDRS letters **, n	514	391	256	181	84	41	7
-%	17	20	21	23	24	26	21
Second eyes	836	589	396	258	120	36	10
Age							
-Median	81	80	79	79	79	77	77
-IQR	76–85	76–84	75–84	75–83	74–83	75–80	75–79
-Range	54–96	54–96	54–95	54–93	54–90	65–86	75–85
Females	607	442	299	189	93	31	10
-%	73	75	76	73	78	86	100
Baseline VA, mean	59	63	65	66	66	67	63
-SD	19	15	14	14	13	14	20
Eyes with VA ≤35 ETDRS letters *, n	71	21	9	5	2	1	1
-%	9	4	2	2	2	3	3
Eyes with VA ≥70 ETDRS letters **, n	230	182	147	100	49	15	5
-%	28	31	37	39	41	42	50

IQR, interquartile range; VA, visual acuity; SD, standard deviation; *Snellen equivalent ≤20/200 Snellen; **Snellen equivalent ≥ 20/40 Snellen.

Supplementary table 2. Mean change of VA and proportion of eyes continuing follow-up from baseline.

Year completers																										
		1				2				3				5				7				10				
	n	Base line VA	n	%	Base line VA	Change in VA	n	%	Base line VA	Change in VA	n	%	Base line VA	Change in VA	n	%	Base line VA	Change in VA	n	%	Base line VA	Change in VA	n	%	Base line VA	Change in VA
All eyes	3 780	55	2 553		59	+2	1 615		61	+2	1055		62	0	470		63	-2	194		62	-2	43		61	-4
1st eye	2 967	54	1 964		58	+3	1 219		60	+2	797		60	0	349		62	-2	158		61	0	33		60	-2
2nd eye	813	59	589		63	0	396		65	-1	258		66	-2	121		66	-2	36		67	-10	10		63	-12
Baseline VA ETDRS letters																										
<35	452	12	142	31	14	+25	66	15	13	+32	40	9	12	+31	11	2	11	+42	7	2	13	+43	2	0.4	20	+25
35-<60	1 265	46	817	65	47	+6	487	38	48	+8	302	27	48	+7	123	10	50	+7	57	5	48	+11	14	1	47	+12
60-<70	1 319	65	1 021	77	65	0	659	50	66	-1	432	33	66	-3	203	15	66	-3	74	6	66	-5	15	1	66	-4
≥70	744	77	573	77	77	-4	403	54	77	-7	281	38	77	-9	133	18	77	-12	56	8	77	-16	12	2	76	-28
All eyes stratified by treatment starting year																										
2008	155	51	118	76	53	+2	71	46	55	+2	48	31	56	-1	29	19	59	-4	14	9	59	-6	6	4	62	-10
2009	176	51	114	65	56	+1	76	43	57	+1	60	34	56	-1	36	20	62	-1	21	12	63	-1	15	9	64	-9
2010	204	54	159	78	55	+1	112	55	57	+2	88	43	59	-1	55	27	60	-2	41	20	59	1	22	11	58	0
2011	224	52	162	72	55	+2	113	50	58	+2	78	35	61	-1	49	22	62	-4	32	14	62	-4	-	-	-	-
2012	288	54	227	79	58	+1	154	53	61	+2	114	40	61	0	73	25	63	-1	38	13	63	-1	-	-	-	-
2013	336	56	238	71	60	+2	169	50	62	+2	118	35	63	-1	68	20	65	0	38	11	65	-3	-	-	-	-
2014	373	56	266	71	60	+2	178	48	61	+1	138	37	62	-1	79	21	65	-1	-	-	-	-	-	-	-	-
2015	311	57	228	73	61	+3	162	52	63	0	137	44	63	-1	81	26	65	-5	-	-	-	-	-	-	-	-
2016	377	56	267	71	62	+1	192	51	63	+2	152	40	64	2	-	-	-	-	-	-	-	-	-	-	-	-
2017	301	55	234	78	60	+3	180	60	61	+3	122	41	62	-1	-	-	-	-	-	-	-	-	-	-	-	-
2018	380	56	288	76	62	+2	208	55	63	+1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2019	343	54	252	73	58	+5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2020	312	55	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

VA, visual acuity; ETDRS, Early treatment diabetic retinopathy study

Supplementary table 3. Median number of annual and mean cumulative intravitreal anti-VEGF injections stratified by the year of treatment initiation and baseline visual acuity.												
	Year completers											
	1		2		3		5		7		10	
	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR
1st eye	6	5–8	6	3–7	6	3–7	6	4–7	6	3.75–7	6	1.5–8
2nd eye	6	4–8	5	3–7	6	3–7	6	2.75–7	5	3–6	5	1.5–7
Cumulative IVI count*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1st eye	6.2	2.1	12	4.0	17	5.7	29	8.5	39	12	51	18
2nd eye	5.9	2.1	11	4.3	17	5.9	27	10	38	13	62	11
Treatment starting year												
	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR
2008	5	3–6	4	2–6	4	2–6	7	5–8	6	2–7	4	0–8
2009	6	5–6	5	3–6	5	2–6	7	3–9	4	3–6	6	3–7
2010	6	5–6	5	3–6	7	4–9	7	5–8	6	4–7	5	0–8
2011	6	5–6	6	3–8	7	5–9	6	4–7	5	3–6	–	–
2012	6.5	6–8	7	4–9	6	5–7	6	4–7	6	4–7	–	–
2013	7	6–9	5	3–7	6	3–7	5	3–7	5.5	3–7	–	–
2014	6	5–8	6	3–7	5	3–6	6	3–7	–	–	–	–
2015	6	5–8	6	3–7	5	4–7	6	4–7	–	–	–	–
2016	6	4–7	6	2–7	6	3–7	–	–	–	–	–	–
2017	7	5–9	5	3–7	6	4–8	–	–	–	–	–	–
2018	7	5–8	6	3–8	–	–	–	–	–	–	–	–
2019	7	5–9	–	–	–	–	–	–	–	–	–	–
2020	–	–	–	–	–	–	–	–	–	–	–	–
Baseline VA												
<35	6	4–7	5	3–7	5	3–7	6	4–8	6	4–7	1**	–
35–<60	6	5–8	6	4–7	6	4–7	6	3–8	5	3–7	5.5	3–8
60–<70	6	5–8	6	3–7	6	4–7	6	4–7	6	3–7	5	0–7
≥70	6	4–7	5	3–7	6	3–7	6	3–7	5	4–6	6	4–8

*At end of each year; **n= 2 eyes. MD, median; IQR, interquartile range; SD, standard deviation; IVI, intravitreal injection

Supplementary table 4. Median number of annual and mean cumulative number of non-injection visits stratified by the year of treatment initiation and baseline visual acuity.												
	Year completers											
	1		2		3		5		7		10	
	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR
1st eye	4	3–4	3	2–4	3	2–4	3	2–4	3	2–4	3	2–4
2nd eye	4	3–5	3	2–4	3	2–4	3	2–4	4	3–5	2	2–4
Cumulative visit count*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1st eye	3.7	1.2	6.9	1.9	9.9	2.6	16	3.8	22	4.9	29	6.0
2nd eye	3.9	1.2	7.1	2.0	10	2.6	17	4.2	22	4.5	29	4.3
Treatment starting year												
	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR	MD	IQR
2008	3	3–4	3	2–3	2	2–3	3	2–4	3.5	2–4	3	1–3
2009	3	2–3	2	2–3	2	2–2	3	2–4	4	3–4	4	2–5
2010	3	2–3	2	2–2	3	2–3	3	2–4	3	3–5	2	1–4
2011	3	2–3	3	2–4	3	2–4	3	3–4	3.5	2–4	–	–
2012	4	3–4	3	3–4	3	2–4	3	2–4	3	2–4	–	–
2013	4	3–5	3	2–4	3	3–4	3	2–4	3	2–5	–	–
2014	4	3–4	3	3–4	3	2–4	4	2–5	–	–	–	–
2015	4	3–5	4	3–4	3	2–4	3	2–4	–	–	–	–
2016	4	3–5	3	2–4	4	3–4	–	–	–	–	–	–
2017	4	3–5	4	3–5	3	2–4	–	–	–	–	–	–
2018	4	3–5	4	2–5	–	–	–	–	–	–	–	–
2019	4	3–5	–	–	–	–	–	–	–	–	–	–
2020	–	–	–	–	–	–	–	–	–	–	–	–
Baseline VA												
<35	3	3–4	3	2–3	3	2–4	3	2–4	3	1–4	2**	2–2
35–<60	3	3–4	3	2–4	3	2–4	3	2–4	3	2–4	3	2–5
60–<70	4	3–4	3	2–4	3	2–4	3	2–4	3	2–4	3	2–4
≥70	4	3–5	3	2–4	3	2–4	3	2–4	4	3–4	2.5	1–4

*At end of each year; **n= 2 eyes. MD, median; IQR, interquartile range; SD, standard deviation

Supplementary table 5. Eyes lost to follow-up stratified by cause.												
	Endpoint at year											
	1		2		3		5		7		10	
Eyes initiated treatment. n	3 523		3 170		2 781		2 084		1 389		535	
	N	%	N	%	N	%	N	%	N	%	N	%
Eyes continued treatment	2 618	74	1 691	53	1110	40	495	24	200	14	44	8.2
Lost to follow-up	905	26	1 479	47	1671	60	1 589	76	1 189	86	491	92
Inactivation of disease	165	18	383	26	447	27	416	26	294	25	125	26
Poor treatment result	503	56	702	48	748	45	697	44	521	44	215	44
Poor general health	59	6.5	120	8.1	156	9.3	157	9.9	120	10	53	11
Death*	25	2.8	35	2.4	51	3.1	54	3.4	50	4.2	14	2.9
Patient declined treatment	78	8.6	111	7.5	119	7.1	117	7.4	89	7.5	39	7.9
Other or unknown	75	8.3	128	8.7	150	9.0	148	9.3	115	9.7	45	9.2

*Death within 1 month from last visit

Supplementary table 6. Median days from Last Observation Carried Forward (LOCF) visit to end of index year and percentage of visits within 1-3 months before end of index year.							
Index year	n (eyes)	Days to end of index year from LOCF visit (median)	Interquartile range		% of LOCF visits within 1 month of end of index year	% of LOCF visits within 2 months of end of index year	% of LOCF visits within 3 months of end of index year
			25 percentile	75 percentile			
1	1 964	61	27	105	28	49	66
2	1 219	60	29	113	26	51	66
3	797	66	31	117	24	48	63
5	349	63	30	114	25	45	64
7	158	62	24	103	30	48	68
10	33	93	36	158	17	34	46