RISK FOR LOW VISUAL ACUITY AFTER 1 AND 2 YEARS OF TREATMENT WITH RANIBIZUMAB OR BEVACIZUMAB FOR PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Risk of having visual acuity lower than 60 letters (approximately 20/60 Snellen) after 1 and 2 years of treatment with ranibizumab or bevacizumab for patients with neovascular age-related macular degeneration: An analysis using real world data from the Swedish Macula Register

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Abbreviated title: Risk of low VA after 1-2 years for nAMD

Keywords: neovascular age-related macular degeneration; bevacizumab; choroidal neovascularization; ETDRS; ranibizumab; register data

Summary Statement:

The development of visual acuity (VA) for patients with neovascular age-related macular degeneration treated with ranibizumab or bevacizumab was analyzed using data from the Swedish Macula Register. The treatment maintained the VA level and after 1 and 2 years only 20 % and 40 % of patients required vision rehabilitation.

Abstract:

Purpose: To investigate how patients with neovascular age-related macular degeneration (neovascular AMD) treated with ranibizumab or bevacizumab respond to treatment in daily clinical practice.

Methods: Patients' characteristics at first visit, visual acuity (VA), number of injections, and reason for terminating the treatment if applicable are discussed. Furthermore, the risk of having poor vision (VA under 60 ETDRS letters or approximately 20/60 Snellen) is calculated for the treated eye after 1 and 2 years.

Patients: Data from the Swedish Macula Register on the treatment received by 3 912 patients during 2011-2014 is reported.

Results: The treatment outcome depends on the VA at first visit. For patients with VA more than 60 letters, the risk of having a VA lower than 60 letters after 1 or 2 years of treatment is around 20 %. However, for patients with low VA at diagnostic (less than 60 letters) the risk is around 60 %. The risk of having VA lower than 60 letters does not depend on the choice of treatment drug.

Conclusion: Treatment with anti-vascular endothelial growth factor intravitreal injections mainly maintains the VA level and only around 20 % and 40 % of the patients required vision rehabilitation after 1 and 2 years, respectively.

Neovascular age-related macular degeneration (neovascular AMD) is one of the leading causes of visual impairment in the elderly population in the Western World[1]. The standard treatment for patients with neovascular AMD is anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections. At the moment, there are two different drugs approved to treat neovascular AMD: ranibizumab (Lucentis, Genentech Inc., South San Francisco, California, USA) and aflibercept (Eylea, Bayer Pharma AG., Berlin, Germany). In clinical trials, both drugs have demonstrated positive effects in maintaining and, in some cases, improving patients visual acuity after 1 and 2 years of treatment[2–4]. In clinical practice, the off-label drug bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA) is also widely employed to treat patients with neovascular AMD. Bevacizumab has significantly lower cost per dose compared with aflibercept and ranibizumab[5]. Two clinical trials compared ranibizumab and bevacizumab using different treatment frequencies showing that bevacizumab was not inferior to ranibizumab if applied with the same frequency[6–8]. Several observational studies followed the first clinical trials and were undertaken in settings similar to daily clinical practice[9–12]. These studies did not show as large beneficial effects as the mentioned clinical trials. Therefore, the size of the benefit experienced by the patients and the optimal treatment setting in daily clinical practice are still not completely established.

The aim of this study is to add further knowledge about how patients with neovascular AMD are treated in daily clinical practice and the results of the treatment. Information about the treatment received by 3 912 patients with neovascular AMD in Sweden during the period 2011-2014 is presented. The data is obtained from the Swedish Macula Register (SMR). This register collects information about most patients treated in Sweden for neovascular AMD from the first visit (diagnostic visit) until the patient finishes receiving treatment. This study focused on patients treated with either ranibizumab or bevacizumab that had their diagnostic visit in the period 2011-2012. The records of those patients were followed until 2014, thus obtaining a two year follow-up period. Data for patients' characteristics at the first visit, changes in visual acuity (VA) at 1 and 2 years after starting the treatment, number of injections received over time and the reason for terminating the treatment if applicable are presented. The risk of having poor vision (VA under 60 Early Treatment Diabetes Retinopathy Study (ETDRS) letters or approximately 20/60 Snellen) for the treated eye after 1 and 2 years of treatment is estimated. The number of patients that need visual rehabilitation after 1 and 2 years is also calculated. In the text VA less or equal to 60 ETDRS letters or approximately 20/60 Snellen will be referred to as VA ≤ 60 letters.

Methods

Study Design and Cohort

This project was approved by the Lund University Ethical Board in September 2015 (Dnr 2015/679). The data was obtained from the SMR, after approval from its steering committee. The Swedish Macula Register started collecting information about treatment of intravitreal injections in 2008. The register is financed by the Swedish Association of Local Authorities and Regions and collects data from patients treated for neovascular AMD from several medical centers across Sweden for both quality improvement and research purposes. The participating centers are privately or publicly owned. The patients attending those centers come from all socioeconomic statuses since treatment for neovascular AMD is fully reimbursed within the public health care system for Swedish residents. When attending the clinic, the patients are informed about the register and only data from those that agree to be part of the register are collected. Some of the variables recorded by the register are the patient's unique personal identity number, visit dates, received treatment, VA for both the treated and the

fellow eye, retina status at diagnosis, and reason to end of treatment. It is worth noticing that the Swedish Macula Register does not required the registration of the best corrected visual acuity (BCVA). However, our experience indicates that most nurses and doctors do register BCVA. The coverage during the period 2011 to 2014 is around 80 %, meaning that approximately 80 % of all patients treated in Sweden for neovascular AMD have records in SMR. The data obtained from SMR was further linked to the Swedish People and Address Register (SPAR) managed by the Swedish Tax Office, in order to get information about the death date if applicable.

Data were collected for all patients for whom their first visit (visit at which the patient was diagnosed with neovascular AMD) took place in the period 1st January 2011 until 31th October 2012 (see Figure 1). During this period most patients were treated with bevacizumab or ranibizumab. The sample included all visit records for those patients until 31th December 2014, in order to get a complete 2 years follow-up period.

Exclusion of data: in this study, we excluded those eyes that were treated previously for neovascular AMD and those that switched treatment drug, for example received first bevacizumab and then ranibizumab. Eyes with incomplete VA assessment at the first visit and patients that were not found in the Swedish People and Address Register were also excluded from the analysis. Finally, our dataset included 3 365 and 547 eyes only treated with ranibizumab and bevacizumab, respectively.

Outcome Measurements

The visual acuity at the first visit (baseline) and after 1 and 2 years for the treated eye, the number of injections received by the patient over time and the reason for discontinuing the treatment if applicable are reported. The number of patients with VA ≥ 60 letters for both eyes at the beginning of the treatment, and after 1 and 2 years are also listed. The first year visit is defined as the latest visit in the period 10 to 14 months after the first visit. The second year visit is defined as the latest visit in the period 22 to 26 months from the first visit. We mostly discuss the results obtained including only patients that continued the treatment and have a complete follow-up (similar to per protocol population). For comparison purposes, the same analyses are presented for all patients in the cohort, including those that don't have a 1 and/or a 2 years visit (similar to the intention to treat population).

Some eyes did not have ETDRS values but had Snellen values and those were converted to ETDRS according to Gregori et al[13]. In total, approximately 15 % of the ETDRS values were converted from Snellen values.

Statistical Analyses

In order to describe the study population the median was used as a tendency parameter, since the distributions were skewed. The standard deviation was reported as a measure of the spread of the distributions. The risk of getting VA ≤ 60 letters for the treated eye at 1 and 2 years after treatment start was calculated using a generalized linear model. Briefly, GLM is a technique used to calculate the probability of an outcome, in this case getting VA ≤ 60 letters, taking into account simultaneously several risk factors, such as age and amount of injections. In this study, we analyzed the total number of injection received during the first year and the first two years. To minimize the risk of introducing immortal bias in the results[14] we avoided analyzing the number of injections received only during the second year. Immortal bias could be caused by not including those patients that did not respond to treatment and that did not get treatment during the second year. In this case, there is a risk that over-

rated results are obtained since patients with deteriorated VA are not included in the analysis for the second year of treatment. Some patients were treated on both eyes (approximately 5 % bilateral cases) and therefore the intragroup correlation was taken into account in the models.

The most frequently used link functions are the logit-link, the probit-link and the log-link. The logit and probit functions behave well numerically, however the interpretation of the results is not straightforward. On the other hand, the log-link has the advantage that it allows interpreting the model coefficients directly in terms of relative risk. When the log link is used, the fitted probabilities may exceed 1, although this problem rarely occurs in practice[15]. In order to facilitate the interpretation of the results, we applied the log-link function in the model. For all analyses the statistical significant level was set at 5 % and the p-values are two-sided.

To enable finding a suitable statistical model, the data was divided into patients that had VA less or equal than 60 letters at the first visit and patients that had VA more than 60 letters at the first visit. The reason to fit different models was that the effect of getting more treatment on the risk of getting VA ≤ 60 letters was different for these groups. One model was fitted to calculate the risk of having VA ≤ 60 letters after 1 year of treatment and another for the 2 years of treatment.

The goal of the statistical analysis was to find models that fitted the data adequately and had clear clinical interpretation. For all cases, the final model was selected after performing several steps. First we included as explanatory variables all the registered variables that we considered could affect the risk of having VA ≤ 60 letters at the end of the treatment year. The first model included a binary variable to indicate whether the patient was older than 79 years when starting the treatment, an indicator variable to describe whether the patient got more than the median number of injections during the treatment year (first year and up to two years), a categorical variable indicating the retina status at the first visit, an indicator variable for treatment drug, and a categorical variable indicating the duration of the symptoms before starting treatment. The variables that were not statistically significant were removed one by one, and the model was refitted with the remaining variables. The final model only contained those variables found to be statistically significant. The remaining variables in the models were the indicator variables age (younger/older than 79 years) and whether the patient got more injections that the median for the corresponding treatment year. The models were validated using a residual analysis.

Results

Study Population and Baseline Characteristics

There were 3 365 and 547 eyes only treated with ranibizumab and bevacizumab, respectively. The treatment received by the patients was decided by the physician and was influenced by several factors such as patients' characteristics, routines in the clinic, availability of the treatment drug, costs, etc. The main characteristics of the patients were similar for both treatment arms (see Table 1). The median age of the patients was around 79 years old and above 60 % of the patients were women. Approximately 40 % of the patients experienced neovascular AMD symptoms for less than 2 months before their first visit. The most frequent retina status at the first visit was 100 % occult lesions (approximately 35 % of the patients) followed by dominantly classic lesions (approximately 25 % of the patients). The VA at first visit was also similar for both treatment groups (see Table 2). The median

number of letters was approximately 58 with a large spread of values (standard deviation 15 letters). Around 57 % of the patients saw 60 letters or fewer at their first visit.

One year follow-up

The results obtained after one year follow-up treatment are listed in Table 2. Also in this case, the values were similar for both treatment groups. After one year, the median total number of injections for the patients with complete one year follow up data was 5 with a large standard deviation, meaning that some patients got more than 5 injections while others got fewer. The median VA was approximately 65 letters (standard deviation approx. 17 letters) for both treatment groups. The median difference in VA between the 1 year visit and the baseline visit was + 3 letters. However the variation between the patients was substantial (standard deviation approximately 15 letters). After one year of treatment around 40 % of the eyes had VA ≤ 60 letters. Twenty-seven percent of the treated patients improved their VA more than 10 letters while around 15 % of the eyes improved their VA more than 15 letters. Eighteen percent of the treated patients lost more than 10 letters while around 12 % of the eyes lost more than 15 letters.

The reasons why patients were lost to follow-up are listed in Table 3. There were 1 041 (31 %) and 131 (24 %) eyes without a complete one year follow up for the ranibizumab and bevacizumab groups, respectively. The most frequent reasons were termination due to low VA, paused without specific reason, and missing values (see Table 3).

Two years follow-up

The results obtained after two years of treatment are listed in Table 2. As for the one year follow-up outcomes, the results were similar for both treatment groups. The median total number of injections received during two years (first year plus second year) for the patients with complete two years follow up was 7 (standard deviation 3.2 injections) and 8 (standard deviation 4.5 injections) for the ranibizumab group and bevacizumab group, respectively. The median VA was approximately 65 letters (standard deviation approx. 17 letters) for both treatment groups. The median difference in VA between the two years visit and the baseline visit was + 2 and + 1 for the ranibizumab group and bevacizumab group, respectively. However the variation between the patients was large (standard deviation approximately 16 letters). After two years of treatment around 40 % of the eyes had VA ≤ 60 letters. For the patients treated with ranibizumab, 26 % improved their VA more than 10 letters while around 15 % of the eyes improved their VA more than 15 letters. Twenty percent of the treated patients lost more than 10 letters while around 13 % of the eyes lost more than 15 letters. For those treated with bevacizumab, around 24 % improved their VA more than 10 letters while around 14 % of the eyes improved their VA more than 15 letters. Twenty-two percent of the treated patients lost more than 10 letters while around 16 % of the eyes lost more than 15 letters.

There were 1 882 (56 %) and 242 (44 %) eyes without a complete two years follow up for ranibizumab group and bevacizumab group, respectively. The most frequent reasons for lost to follow-up at two years are similar to those for one year follow-up: termination due to low VA, paused without specific reason, and missing values (see Table 3).

Risk for having VA ≤ 60 letters (approximately 20/60 Snellen) after one and two years of treatment

In order to estimate the risk of low VA two statistical models were calculated: one for patients with low VA at baseline and another one for patients with high VA at baseline. Furthermore, one model calculated the risk of having VA ≤ 60 letters after 1 year of treatment and another model calculated the risk after 2 years of treatment. In total, four statistical models were calculated. The results are listed in Table 4.

In the case of patients with VA ≤ 60 letters, the results were similar after one and two years of treatment. The crude risk (risk without taking into account any explanatory factors) for maintaining a low VA after one year of treatment is 0.64 (95 % CI 0.619; 0.670) with p-value < 0.0001 (see Table 4). This indicates that after one year of treatment around 64 % of the patients would still have a low VA. After two years of treatment, the crude risk is 0.61 (95 % CI 0.582; 0.649) with p-value < 0.0001, meaning that around 61 % of the patients that complete two years of treatment would have a low VA.

In order to estimate how the risk of having low VA is affected by treatment drug, age, and the total number of injections received, a model was calculated including those variables as explanatory variables. There were no statistical significant difference in the risk of having VA ≤ 60 letters for patients that got bevacizumab compared with those treated with ranibizumab (risk for one year: 1.0 (95 % CI 0.900; 1.113) p-value = 0.983, risk for two years: 1.08 (95 % CI 0 .941; 1.236) p-value = 0.280). In other words, our results indicate that for patients with similar age (older/younger than 79 years) and number of injections receiving bevacizumab did not affect the risk compared with those that got ranibizumab.

To obtain more efficient estimates for the effect of age and number of injections, we removed the variable treatment from the statistical model and calculated a new model (see Table 4). As expected, an increase in age is associated with an increase in the risk of maintaining a low VA (risk for one year: 1.18 (95 % CI 1.082; 1.290) p-value < 0.0001, risk for two years: 1.11 (95 % CI 0.983; 1.244) p-value=0.095). Patients older than 79 years old have an approximately 18 % higher risk of maintaining low VA compared with those younger than 79 years. After two years, patients older than 79 years have approximately 11 % increased risk compared with younger patients, although it is not statistically significant. Receiving more than 5 injections does not affect the risk of remaining with low VA (risk after one year of treatment: 1.04 (95 % CI 0.960; 1.119) p-value =0.369, after two years of treatment 0.94 (95 % CI 0 .839; 1.045) p-value = 0.242).

Similar models were fitted using data for patients that had VA > 60 letters at the first visit (see Table 4). The crude risk was 0.20 (95 % CI 0.178; 0.221) with p-value < 0.0001 and 0.25 (95 % CI 0.228; 0.283) with p-value < 0.0001, for patients with a complete one and two years follow up respectively. This indicates that approximately 20 % and 25 % of patients would have a low VA after 1 and 2 years of treatment, respectively.

Also in this case, we do not observe a statistically significant difference in risk for patients treated with bevacizumab compared with those treated with ranibizumab (risk for one year: 0.77 (95 % CI 0.554; 1.079) p-value= 0.131, risk for two years: 1.00 (95 % CI 0.750; 1.322) p-value = 0.977).

An increase in age has a negative effect on VA. After one and two years of treatment, patients older than 79 years would have approximately 49 % (1.49 (1.198; 1.857) p-value < 0.0001) and 38 % (1.38 (1.108; 1.717) p-value = 0.004) higher risk of low VA compared with younger patients, respectively (see Table 4). For patients with higher VA at the first visit, receiving more than 5 injections does affect the risk of getting a low VA after one year of treatment (1.45 (95 % CI 1.150; 1.820) p-value = 0.002). Patients that got more than 5 injections during the first year had 45 % statistically significant increased risk of getting low VA compare to those that got fewer injections. After two years of treatment, patients that got fewer than 7 injections during two years do not have statistically significant higher risk compared with those receiving less treatment (1.10 (95 % CI 0.882; 1.364) p-value=0.406).

Estimated number of patients that need vision rehabilitation after one and two years of treatment

In Sweden, low vision centers provide visual rehabilitation in case of visual acuity of the best-seeing eye being less or equal than 60 letters ETDRS or approximately 20/60 Snellen, significantly restricted visual fields or presence of homonymous hemianopia. Patients fulfilling these conditions are entitled a referral to a vision rehabilitation center. The number of patients with VA less than 60 letters on both eyes is calculated. After one year of treatment, 750 (22 %) patients treated with ranibizumab were entitled to vision rehabilitation. For those treated with bevacizumab, 129 (24 %) needed vision rehabilitation. At the end of the two years period there were 1197 (36 %) patients treated with ranibizumab and 218 (40 %) treated with bevacizumab that needed vision rehabilitation.

Discussion

In this article information about the treatment given to patients diagnosed with neovascular AMD during 2011-2012 with a 2 years follow up period is presented using real world data from the Swedish Macula Register. The change in VA at 1 year had a median of + 3 letters and a standard deviation of 15 letters for patients treated with ranibizumab or bevacizumab. At 2 years the change in VA from the first visit had a median of + 2 (ranibizumab) and + 1 (bevacizumab) letters and standard deviation of 17 letters. For both time points there was a large spread indicating that some patients improved their VA while others got a lower VA value. As expected, the effect of age is negative for the development of VA. It could be due to biological reasons but also due to the difficulties to attend to the eye clinic due to other diseases that may be present at higher age. After 1 and 2 years of treatment, around 20 % and 40 % of the patients required vision rehabilitation, respectively.

The efficacy of ranibizumab for the treatment of neovascular AMD was shown in several clinical trials[2,3,9,12,16,17]. The MARINA clinical trial compared ranibizumab against placebo in 716 patients[3]. The authors observed that VA improved by 15 or more letters in about 25 % - 34 % of the study population and the VA mean increased was about 6.5 -7 letters after 1 and 2 years follow up. The ANCHOR study compared ranibizumab against verteporfin photodynamic therapy (PDT) including 423 patients with neovascular AMD[2] with 1 and 2 year follow up. About 34 % to 41 % of the patients treated with ranibizumab had gained more than 15 letters and, on average, VA was improved from baseline by 8.1 to 10.7 letters. Similar results were obtained in the FOCUS trial with 162 patients[16]. Some clinical trials that compared bevacizumab with ranibizumab showed that the two drugs have similar efficacy if applied in similar way[6–8]. The CATT and IVAN trials compared the effect of bevacizumab with the effect of ranibizumab at 1 and 2 years follow up[6,7]. The CATT trial found that patients VA improved on average 6.8 and 8.5 letters with ranibizumab ordered monthly and as needed respectively[7]. The VA of patients receiving bevacizumab improved on average 8 and 5.9 letters for those following monthly and as needed regime, respectively[7]. The IVAN trial reported that after 2 years follow up, the VA of patients receiving ranibizumab improved 4.9 letters on average while the VA of patients receiving bevacizumab improved 4.1 letters on average[6]. Our results regarding the improvement in VA are lower compared with those reported in clinical trials (see Figure 2). Other observational studies also found lower VA improvement[10–12]. These differences could be due to different treatment programs and differences between the study populations. The patients participating in the mentioned clinical trials were specially recruited, got closer follow up, and larger amount of injections compared with the patients in this study. In general, patients enrolled in clinical trials are carefully selected and follow a strict treatment program while our study included an unselected population treated in standard clinical practice. In the CATT and IVAN studies, the authors found that patients that received more injections showed slightly better functional outcomes[6,7]. These findings suggest that increasing the treatment

frequency improves the VA. The patients in this study received on average fewer injections compared with the mentioned clinical trials, which probably had an effect on the development of the VA. Our results are consistent with the finding observed in the clinical trials comparing the effect of ranibizumab and bevacizumab since we are unable to observe any clinical or statistically significant differences between the patients who received ranibizumab and those who got bevacizumab.

AURA was an observational multi-country study including 2 227 patients treated with ranibizumab in standard clinical practice[11]. The authors found that the number of injections given in clinical practice is less than in clinical trials (mean injections at 1 year = 5 and at 2 years = 2.2) and that the mean change in VA was + 2.4 and + 0.6 letters at 1 and 2 years respectively. Holz et al[11] also found that more frequent visits and injections were associated with greater improvement in VA. Our results are similar to those reported in AURA regarding VA and the number of injections. However, we don't observe a protective effect of the number of injections in VA. Injections less than once a month result in a small decrease in mean VA, shown in CATT and IVAN trials. Fewer injections year one and especially year 2 in our study could have an effect on the VA results and explain the inability to maintain VA Year 2. These differences could also be due to differences in the patient population and in the clinical routines in Sweden compared with the countries that participated in AURA.

It is worth noticing that since our data is observational it is not possible from our results to imply causal association between the number of received injections and the development of the VA. Our results indicate that for patients with fewer than 60 letters VA at baseline, getting more than 5 injections during the first year or more than 7 (ranibizumab) or 8 (bevacizumab) injections during the first two years of treatment neither increase nor decrease statistically the risk of remaining with low VA. In other words, our results do not show that patients with low VA at baseline who got more injections performed better than patients who got less injections. For patients with VA > 60 letters at baseline our results indicate that the patients who got more than 5 injections during the first year had between 15 % and 82 % larger risk of getting a VA ≤ 60 letters compared with those patients who got less than 5 injections. A plausible explanation could be that since most doctors would expect patients to maintain their VA with treatment, those receiving more treatment were those that got worse during the treatment year and therefore they had an increased risk of getting VA under 60 at 1 year follow up. Our data does not show neither a protective nor a negative effect of increasing the number of injections to more than 7/8 injections during the first two years of treatment. However, since several parameters that may affect the development of the disease, such as severity, are not included in our model, it is not possible to separate this effect from the effect given by treatment frequency in the development of the VA. Therefore, our results are inconclusive regarding the effect of the injections and further research about the optimal number of injections for different group of patients in standard clinical practice is needed.

The analyses presented here have several limitations. Our results are based on register data, which is neither totally complete nor correct. The Swedish Macula Register estimates errors and missing values to be around 5 %, 1 % and 13 % for ETDRS, number of injections, and Snellen respectively. Approximately 15 % of the ETDRS values were converted from Snellen, which could introduce errors in particularly at low VA. Not all the patients had a complete follow up at 1 and 2 years. There are 2 740 (70 %) of the eyes with a complete 1 year follow up visit and 1 788 (45 %) of the eyes with a complete 2 years follow up visit. Some patients died before the 1 and 2 years periods were completed (4 % at 1 year and 9 % at 2 years). We addressed these difficulties by performing the analysis in two different datasets, one with the complete data and the other with the available data. Since the results are similar for both datasets, we believe that the bias effects due to missing data and misclassifications probably are negligible. In order to obtain a model that fitted the data adequately, only the variables

recorded in the register were used. The VA could be affected by other variables such as severity of the disease, activity in the retina, etc., that are not collected by the SMR and could be important for the estimation of the risk to have VA ≤ 60 letters. Additionally, since the analyses are performed using a large database, some parameters might be statistically significant just due to the large amount of included patients. To determine which parameters are clinically significant, we present the confidence intervals together with the p-values in order to clearly state the range of plausible values for the calculated parameters.

One of the main advantages of our study is that a very large number of eyes is included in the analysis. Furthermore, our results are obtained using an unselected population. The risk estimates presented here are obtained using most of the patients that got treatment for neovascular AMD in Sweden. We also obtained similar results when using the complete data set (similar to intention to treat population) or only those patients that had a complete follow up (similar to per protocol population).

Overall, we observed that the treatment with anti-VEG drugs helps patients to maintain their VA level which is an important progress in the treatment of neovascular AMD. The treatment outcome largely depends on the VA of the patient at the first visit. For those patients with VA > 60 letters, the risk of having a VA ≤ 60 letters after 1 or 2 years of treatment is around 20 %. On the other hand, for patients with low VA at diagnostic (≤ 60 letters) the probability of getting a VA ≤ 60 letters is around 60 % after 1 or 2 years of treatment. Our study also indicates that the risk of having VA ≤ 60 letters is independent of the treatment drug, meaning that in our population patients treated with bevacizumab have similar risk compared with those treated with ranibizumab. As expected, the risk of low VA depends on the age of the patient, older patients have a higher risk compared with younger patients.

The effect of the number of injections on VA in standard clinical practice is not well established. Clinical trials suggest that patients receiving monthly injections had slightly better outcomes compared with patients treated as needed[6,7]. Our results may indicate that the effect of the number of injections in VA could be related to the VA level of the patients when they start the treatment. For patients with VA ≤ 60 letters at baseline, the risk of low VA after 1 and 2 year of treatment is similar for all patients regarding the number of received injections. On the other hand, for patients with VA > 60 letters at baseline, there seems to be a negative association between the number of injections and the risk of getting a lower VA. It is observed that patients who got more injections have developed worse compared with those who got fewer injections. This negative association is counterintuitive. However, since it is not possible to account for potential confounding factors such as disease severity in our analysis, further studies are needed in order to assess the optimal number of injections in standard clinical practice for different patients´ groups. Only around 20 % and 40 % of the patients required vision rehabilitation after 1 and 2 years, respectively, which is a great progress in the treatment of neovascular AMD. Our findings thus provide valuable information when communicating with patients and for planning purposes in the healthcare system.

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Figure 1: Selection of the patients.

Figure 2: Bar graphs (A and B) showing percentage of eyes with ETDRS letter gain/loss and line graphs (C) showing the mean VA in SMR study compared to clinical trials CATT[7] and IVAN[6] by drug assigned over time.

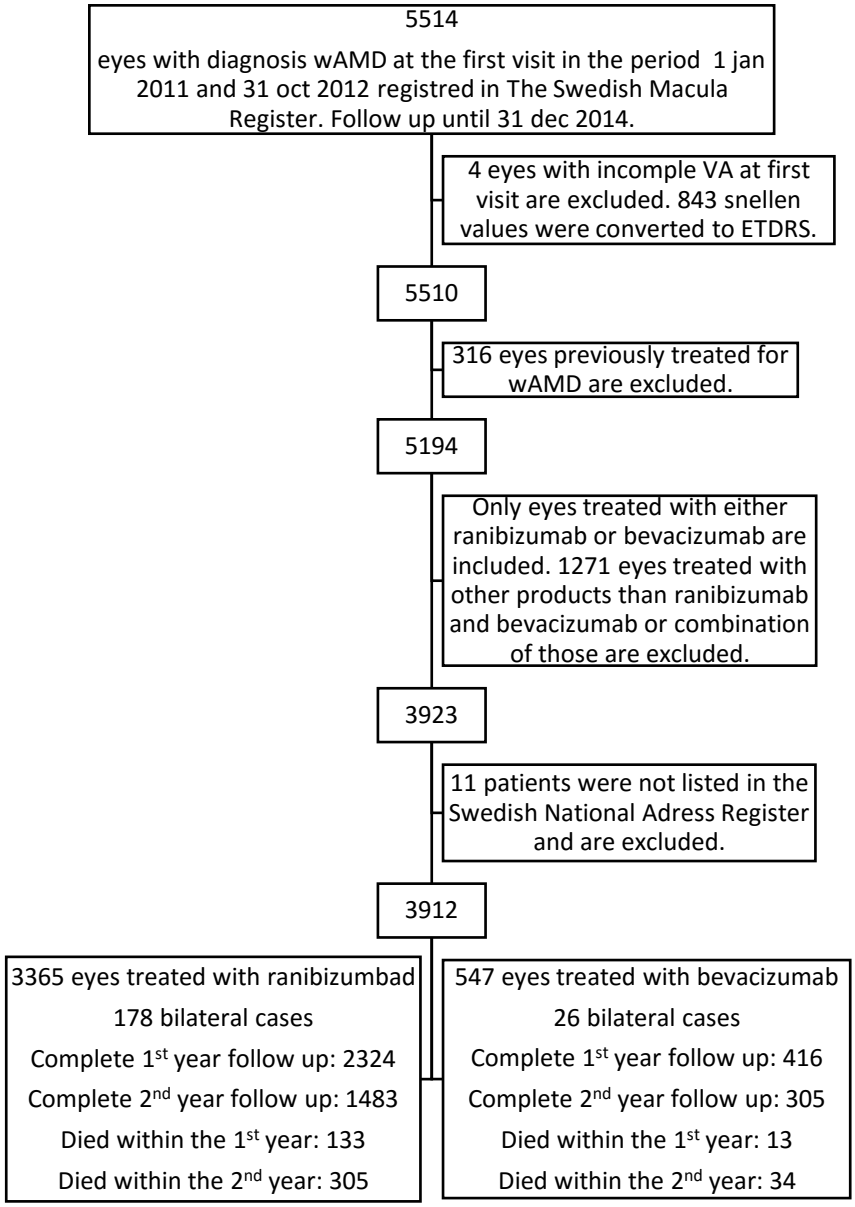

5514
eyes with diagnosis wAMD at the first visit in the period 1 jan 2011 and 31 oct 2012 registred in The Swedish Macula Register. Follow up until 31 dec 2014.
4 eyes with incomple VA at first visit are excluded. 843 snellen values were converted to ETDRS.
5510
316 eyes previously treated for wAMD are excluded.
5194
Only eyes treated with either ranibizumab or bevacizumab are included. 1271 eyes treated with other products than ranibizumab and bevacizumab or combination of those are excluded.
3923
11 patients were not listed in the Swedish National Adress Register and are excluded.
3912
3365 eyes treated with ranibizumbad
178 bilateral cases
Complete 1st year follow up: 2324
Complete 2nd year follow up: 1483
Died within the 1st year: 133
Died within the 2nd year: 305
547 eyes treated with bevacizumab
26 bilateral cases
Complete 1st year follow up: 416
Complete 2nd year follow up: 305
Died within the 1st year: 13
Died within the 2nd year: 34

Table 1: Parameters at first visit. *PCV: polypoidal choroidal vasculopathy, †RAP: retinal angiomatous proliferation. The first visit is defined as the visit in which the patient was diagnosed with neovascular AMD. Patients with a complete 1 year follow up have a visit in the period 10-14 months from the first visit. Patients with a complete 2 years follow up have a visit in the period 22-26 months.

		All patients		Patients with a complete 1 year follow up		Patients with a complete 2 years follow up	
Parameter		Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab
Number of eyes		3365	547	2324	416	1483	305
Bilateral cases		178	26	110	18	76	9
Age at first visit (years)	Median	80. 4	80.6	79.7	80.3	79.4	79.8
	Sd	8.3	8.2	8.3	8.2	7.8	8.3
Sex	Female	2254 (67.0 %)	339 (62.0 %)	1545 (66.4 %)	256 (61.5 %)	1003 (67.3 %)	184 (60.3 %)
	Male	1111 (33.0 %)	208 (38.0 %)	779 (33.5 %)	160 (38.5 %)	480 (32.7 %)	121 (39.8 %)
Symptoms' duration before first visit	0 up to 2 months	1249 (42.5 %)	270 (49.4 %)	1005 (43.2 %)	205 (49.3 %)	630 (42.5 %)	161 (52.8 %)
	2 up to 4 months	890 (26.4 %)	120 (21.9 %)	596 (25.7 %)	91 (21.8 %)	385 (26.0 %)	64 (21.0 %)
	4 up to 6 months	525 (15.6 %)	65 (11.9 %)	358 (15.4 %)	49 (11.8 %)	220 (14.8 %)	32 (10.5 %)
	More than 6 months	521(15.5 %)	92 (16.8 %)	365 (15.7 %)	71 (17.7 %)	248 (16.7 %)	48 (15.7 %)
Retina's status at first visit	Minimally classic lesions	319 (9.5 %)	47 (8.6 %)	215 (9.3 %)	35 (8.5 %)	134 (9.0 %)	24 (7.9 %)
	Dominantly classic lesions	840 (25.0 %)	114 (20.8 %)	560 (24.1 %)	88 (21.2 %)	341 (23.0 %)	67 (22.0 %)
	100 % occult lesions	1219 (36.2 %)	226 (41.3 %)	878 (37.8 %)	179 (43.0 %)	588 (39.7 %)	127 (41.6 %)
	*PCV	39(1.6 %)	10 (1.8 %)	22 (1.0 %)	5 (1.2 %)	10 (0.7 %)	6 (2.0 %)
	†RAP	487 (14.5 %)	80 (14.6 %)	359 (15.5 %)	62 (14.9 %)	236 (15.9 %)	44 (14.4 %)
	Not possible to determine	460 (13.7 %)	70 (12.8 %)	290 (12.5 %)	47 (11.3 %)	174 (11.7 %)	37 (12.1 %)

Table 2: Visual acuity at first visit, 1 and 2 years follow up for different patients' cohorts. The first visit is defined as the visit in which the patient was diagnosed with neovascular AMD. For all patients, the 1st year visit is defined as the latest visit up to 14 months from the first visit. The 2nd year visit is defined as the latest visit up to 26 months from the first visit. Patients that have a visit in the period 10 to 14 months from the first visit are considered to have a complete 1 year follow up. Patients that have a visit in the period 22 to 26 months from the first visit are considered to have a complete 2 years follow up. In both cases, the latest visit is considered the follow up visit.

		All patients		Patients with a complete 1 year follow up		Patients a with complete 2 years follow up	
Parameter		Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab
Number of eyes		3365	547	2324	416	1483	305
VA at first visit (ETDRS)	Median	58	59	60	59	63	62
	Sd	15.4	15.1	14.0	14.1	13.3	13.7
Number of eyes with VA less than 60 letters (20/66 Snellen) at first visit		1927 (57.3 %)	311 (56.9 %)	1178 (50.7%)	218 (52.4 %)	657 (44.3 %)	140 (45.9 %)
VA at 1st year of treatment (ETDRS)	Median	60	61	65	64	67	67
	Sd	20.4	19.7	17.8	17.7	14.4	13.6
VA 1st year – VA first visit	Median	1	2	3	3	4	4
	Sd	16.0	15.8	15.0	15.4	13.0	12.6
Number of eyes with VA less than 60 letters (20/66 Snellen) at 1st year of treatment		1665 (49.4 %)	265 (48.4 %)	931 (40.6%)	169 (40.6 %)	470 (31.7%)	96 (31.5 %)
Number of patients that improved their VA with 10 letters or more after the 1st year of treatment		777 (23.1 %)	133 (24.3 %)	634 (27.3 %)	115 (27.6 %)	441 (29.7 %)	93 (30.5 %)
Number of patients that improved their VA with 15 letters or more after the 1st year of treatment		444 (13.2 %)	74 (13.5 %)	365 (15.7 %)	68 (16.4 %)	242 (16.3 %)	52 (17.1 %)
Number of patients that worsened their VA with 10 letters or more after the 1st year of treatment		742 (22.1 %)	108 (19.7 %)	431 (18.6 %)	71 (17.1 %)	193 (13.0 %)	34 (11.2 %)
Number of patients that worsened their VA with 15 letters or more after the 1st year of treatment		521 (15.5 %)	73 (13.4 %)	278 (12.0 %)	48 (11.5 %)	103 (7.0 %)	18 (5.9 %)
Number of injections received during the 1st year of treatment	Median	4	4	5	5	5	5
	Sd	2.0	2.7	1.9	2.7	1.9	2.7
VA at 2nd year of treatment (ETDRS)	Median	58	57	62	61	65	64

	Sd	21.3	21.1	19.8	20.0	16.7	16.7
VA 2nd year – VA first visit	Median	0	0	1	1	2	1
	Sd	17.9	18.1	17.5	18.1	16.1	15.7
Number of eyes with VA ≤ 60 letters (20/66 Snellen) at 2nd year of treatment		1800 (40.1 %)	297 (54.3 %)	1068 (46.0%)	200 (48.1%)	582 (39.2 %)	127 (41.6 %)
Number of patients that improved their VA with 10 letters or more after the 2nd year of treatment		720 (21.4 %)	112 (20.5 %)	573 (24.5 %)	96 (23.1 %)	388 (26.2 %)	75 (24.6 %)
Number of patients that improved their VA with 15 letters or more after the 2nd year of treatment		419 (12.5 %)	64 (11.7 %)	334 (14.4 %)	57 (13.7 %)	224 (15.1 %)	44 (14.4 %)
Number of patients that worsened their VA with 10 letters or more after the 2nd year of treatment		904 (26.9 %)	149 (27.2 %)	577 (24.8 %)	110 (26.5 %)	299 (20.2 %)	67 (22.0 %)
Number of patients that worsened their VA with 15 letters or more after the 2nd year of treatment		663 (19.7 %)	111 (20.3 %)	408 (17.6 %)	83 (20.0 %)	198 (13.4 %)	48 (15.7 %)
Number of injections received from treatment start up to the 2nd year of treatment	Median	4	5	6	7	7	8
	Sd	3.1	4.5	3.2	4.5	3.2	4.5

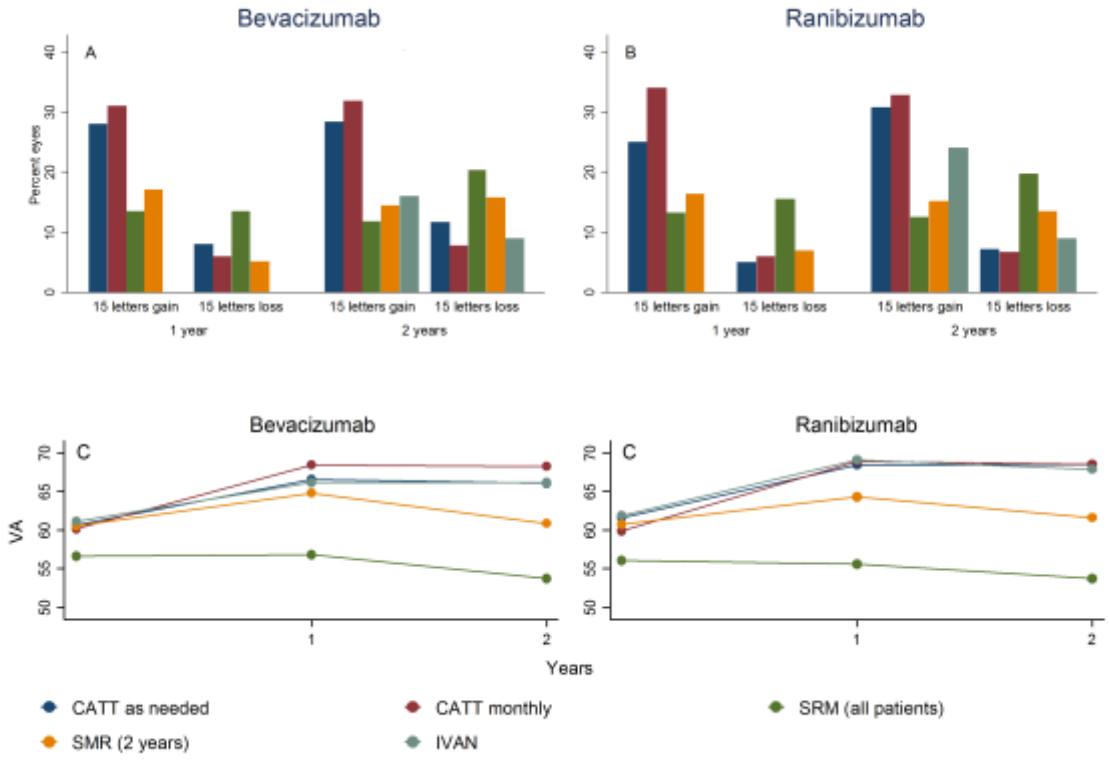
Table 3: Reasons to terminate the treatment

	First year		Second year	
Reasons to terminate the treatment	Ranibizumab	Bevacizumab	Ranibizumab	Bevacizumab
Other reasons	30 (2.9 %)	1 (0.8 %)	80 (4.3 %)	2 (0.8 %)
Terminated-stable	36 (3.5 %)	8 (6.1 %)	288 (15.3 %)	38 (15.7 %)
Terminated-died	133 (12.8 %)	13 (9.9 %)	305 (16.2 %)	34 (14.0 %)
Terminated-negative effects	6 (0.6 %)	1 (0.8 %)	9 (0.5 %)	2 (0.8 %)
Terminated-low VA	239 (23.0 %)	40 (30.5 %)	386 (20.5 %)	70 (28.9 %)
Terminated-patient's decision	21 (2.0 %)	1 (0.8 %)	29 (1.5 %)	4 (1.7 %)
Paused-no indicated	384 (36.9 %)	38 (29.0 %)	567 (30.1 %)	53 (21.9 %)
Paused-infection/other medical reason	2 (0.2 %)	0 (0 %)	2 (0.1 %)	0 (0 %)
Missing values	190 (18.3 %)	29 (22.1 %)	216 (11.5 %)	39 (16.1 %)
Total	1041 (100 %)	131 (100 %)	1882 (100 %)	242 (100 %)

		Risk to have VA less than 60 letters (20/60 Snellen) at 1 year follow up		Risk to have VA less than 60 letters (20/60 Snellen) at 2 years follow up	
		All patients	Patients with complete 1 year follow up	All patients	Patients with complete 2 years follow up
For patients with VA ≤ 60 letters (approximately 20/60 Snellen) at the first visit	Number of eyes	2238	1396	2238	797
	Crude estimate	0.71 (0.694; 0.731) p-value < 0.0001	0.64 (0.619; 0.670) p-value < 0.0001	0.74 (0.723; 0.759) p-value < 0.0001	0.61 (0.582; 0.649) p-value < 0.0001
	Patients older than 79 years compared to patients younger than 79 years	1.09 (1.027; 1.150) p-value = 0.004	1.18 (1.082; 1.290) p-value < 0.0001	1.06 (1.011; 1.122) p-value = 0.018	1.11 (0.983; 1.244) p-value=0.095
	Patients that got more than median number of injections compared to patients that got less than the median number of injections during the treatment period	0.84 (0.797; 0.884) p-value < 0.0001	1.04 (0.960; 1.119) p-value =0.369	0.86 (0.823; 0.905) p-value < 0.0001	0.94 (0.838; 1.043) p-value =0.229
For patients with VA > 60 letters (approximately 20/60 Snellen) at the first visit	Number of eyes	1674	1344	1674	991
	Crude estimate	0.20 (0.182; 0.221) p-value < 0.0001	0.20 (0.178; 0.221) p-value < 0.0001	0.26 (0.242; 0.284) p-value < 0.0001	0.25 (0.228; 0.283) p-value < 0.0001
	Patients older than 79 years compared to patients younger than 79 years	1.51 (1.236; 1.834) p-value < 0.0001	1.49 (1.198; 1.857) p-value < 0.0001	1.40 (1.188; 1.653) p-value < 0.0001	1.38 (1.108; 1.717) p-value=0.004
	Patients that got more than median number of injections compared to patients that got less than the median	1.34 (1.186; 1.652) p-value = 0.006	1.45 (1.150; 1.820) p-value = 0.002	1.39 (1.156; 1.675) p-value <0.0001	1.10 (0.882; 1.364) p-value=0.406

	number of injections during the treatment period				

Table 4: Risk estimates for different cohorts obtained using a generalized linear model. The response variable is a binary variable that indicates whether the VA for the treated eye is less than 60 letters (approximately 20/60 Snellen) at the first/second year follow up. Two binary variables are included in the model as covariates, one indicates whether the patient was older than 79 years old and the other one indicates whether the patient got more than the number of median injection during the first/second year. The results from the crude model (without covariates) are also presented. The first visit is defined as the visit in which the patient was diagnosed with neovascular AMD. For all patients, the 1st year visit is defined as the latest visit up to 14 months from the first visit. The 2nd year visit is defined as the latest visit up to 26 months from the first visit. Patients that have a visit in the period 10 to 14 months from the first visit are considered to have a complete 1 year follow up. Patients that have a visit in the period 22 to 26 months from the first visit are considered to have a complete 2 years follow up. In both cases, the latest visit is considered the follow up visit.


Bevacizumab
Ranibizumab
A
B
C
C
Percent eyes
0
10
20
30
40
15 letters gain
15 letters loss
1 year
2 years
VA
50
55
60
65
70
1
2
Years
CATT as needed
CATT monthly
SRM (all patients)
SMR (2 years)
IVAN