Ten-Year Treatment Outcomes of Neovascular Age-Related Macular Degeneration from Two Regions

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• PURPOSE: To report and compare 10-year treatment outcomes of vascular endothelial growth factor (VEGF) inhibitors for neovascular age-related macular degeneration (nAMD) from Australia and New Zealand (ANZ) and Switzerland.

• DESIGN: Retrospective, comparative, interventional case series.

• METHODS: We analyzed 712 treatment-naive eyes (ANZ, n = 474; Switzerland, n = 321) starting anti-VEGF for nAMD in routine clinical practice between January 1, 2006, and December 31, 2008, tracked in the prospectively designed observational database, the Fight Retinal Blindness! registry. The primary outcome was mean change in visual acuity (VA [in logMAR letters]) in eyes that completed 10 years of treatment.

• RESULTS: The mean VA in 132 eyes (28%) from ANZ patients who completed 10 years of treatment dropped by 0.9 letters from baseline (95% confidence interval [CI], −4.9 to 3.1; $P = 0.7$) with 42% achieving ≥20/40, whereas the 37 eyes (12%) from Swiss subjects lost 14.9 letters (95% CI, −24 to −5.7; $P < 0.001$) with 35% achieving ≥20/40. Eyes from ANZ patients received more injections than eyes from Swiss subjects over 10 years (a median of 53 vs 42, respectively) from fewer visits with better disease control (proportion of visits with active disease: 38% vs 69%, respectively), suggesting a treat-and-extend regimen versus a pro re nata regimen (treatment given only when the lesion is active). Macular atrophy and subretinal fibrosis were the main reasons for 10 letter loss in the subset of eyes analyzed retrospectively. The mean VA of eyes from both regions that discontinued treatment within 10 years had fallen below the baseline at their final visit.

• CONCLUSIONS: Eyes with nAMD may achieve satisfactory long-term visual outcomes if they receive adequate treatment. Central macular atrophy does not develop universally in eyes receiving long-term treatment with VEGF inhibitors as previously feared. Visual outcomes were better in eyes from ANZ patients, likely because they received more injections. (Am J Ophthalmol 2019;■:■–■. © 2019 Elsevier Inc. All rights reserved.)

THE INCIDENCE OF NEOVASCULAR AGE-RELATED macular degeneration (nAMD), a leading cause of blindness in people 50 years of age or older in the developed world, is likely to increase with the progressively ageing population.[1] The pivotal phase 3 studies of intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors that were completed over 10 years ago demonstrated remarkable clinical benefits for neovascular nAMD at 2 years.[2–4] Many practitioners continue to treat eyes indefinitely, but there are limited data for the long-term outcomes.[5–8]

Progression of the non-neovascular components of AMD such as development of macular atrophy may compromise long-term outcomes. Some studies have suggested that more intensive treatment regimens may increase the risk of developing macular atrophy.[9] One of the few reports of 7-year outcomes of treatment of nAMD found macular atrophy had developed in over 90% of eyes.[6] A larger report, which found approximately 40% of eyes had lost central vision due to macular atrophy after 7 years of treatment, suggested that under-treatment was a more significant cause of poor long-term outcomes.[5] The development of subretinal fibrosis may also irreversibly damage vision.

The present study sought to describe 10-year outcomes of treatment with VEGF inhibitors in eyes with nAMD. Preliminary analysis revealed different treatment patterns and outcomes from 2 different regions, Australia and New Zealand (ANZ) and Switzerland, so their outcomes were analyzed separately.

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SUBJECTS AND METHODS

• **STUDY DESIGN:** Data from a prospectively designed, internet-based treatment outcomes registry, the Fight Retinal Blindness! (FRB!) project were analyzed.

• **SETTING:** The FRB! project AMD module database tracked outcomes of treatment of eyes with nAMD. The data analyzed in this study were from participants who were treated for nAMD from practices in Australia, New Zealand, and Switzerland. Institutional ethics approval was obtained from the ethics committees of the University of Sydney, the Royal Australian and New Zealand College of Ophthalmologists, and the Cantonal Ethics Committee Zurich. Ethics committees in Australia and New Zealand approved the use of an "opt out" patient consent. The FRB! study conformed to the provisions of the Declaration of Helsinki.

• **DATA SOURCES AND MEASUREMENTS:** Details of the principles and design of the FRB! registry have been published previously.[10] The number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA chart (best of uncorrected, corrected, or pinhole), activity of the choroidal neovascular membrane, treatment given (if any), and ocular adverse events were recorded at each visit. Treatment decisions, including choice of treatment and visit schedules, were made at the discretion of the treating physician in consultation with the patient, thereby reflecting real world practice.

• **PARTICIPANTS AND VARIABLES:** Treatment naïve eyes with nAMD starting treatment with intravitreal injections of VEGF inhibitors between January 1, 2006, and December 31, 2008, allowing a potential observation period of at least 10 years, were considered for the analysis.

• **OUTCOME MEASUREMENTS:** The main outcome measurement was the mean change in VA from the initial treatment visit (baseline) to 10 years in patients who were followed for at least 10 years. The proportion of eyes with VA of ≥70 letters (20/40 Snellen equivalent, driving vision) and ≤ 35 letters (20/200, legally blind) at 10 years and those that gained ≥10 letters or lost ≥10 letters during the same period were also evaluated.

Other prospectively defined secondary outcomes were the number of injections and the number of visits over the 10-year period. The VA outcome of eyes with good initial vision (≥70 letters [20/40]) and eyes with poor initial vision (≤35 letters [20/200]) were compared with those eyes with a baseline VA of 36 to 69 letters. The VA trends for eyes of patients who were lost during the 10-year follow-up period also were analyzed. These outcomes were assessed in patients from 2 regions, ANZ and Switzerland. The cause of vision loss of ≥10 letters in eyes that received 10 years of treatment was assessed by a selection of practitioners who contributed the most patients based on clinical notes, optical coherence tomography images, which were usually obtained at each visit, as well as fundus autofluorescence images where available.

TABLE 1. Demographic Characteristics of the Eyes Starting Treatment in the 2 Regions

	Australia and New Zealand	Switzerland
Number of eyes	474	321
Number of patients	417	273
Mean ± SD age, y	79.1 ± 7.7	79.3 ± 6.9
Female patients	247 (59.2)	189 (69.2)
Right eye	232 (48.9)	163 (50.8)
Mean ± SD baseline VA letters (logMAR) (Snellen equivalent)	54.4 ± 19.3 (20/80)	52.9 ± 15.5 (20/80)
Lesion type, %[a]		
Occult	49	63
Minimally classic	22	11
Predominantly classic	22	18
Other	7	8

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; VA = visual acuity.

Values are n (%) and mean ± SD.

[a]Lesion type available for 381 Australian and New Zealand eyes and 317 Swiss eyes.

• **STATISTICAL ANALYSIS:** Descriptive data included mean ± SD, median (first and third quartiles, Q1 and Q3), and percentage where appropriate. Change in VA from baseline was analyzed for each year in eyes of patients who completed follow-up visits (completers), in eyes of patients who did not complete follow-up visits (noncompleters), and in all eyes. Noncompleters were grouped according to the year of noncompletion. Outcomes were also investigated in eyes divided by their baseline visual acuity: ≥70 letters (20/40) and ≤35 letters (20/200). Paired *t*-tests were used to determine whether changes in VA at 10 years from baseline were significant. Time to study dropout was analyzed using Kaplan-Meier survival curves.

A longitudinal generalized additive model, including visits from all the eyes regardless of whether they completed 10 years of observations or not, was used for predicting VA over 10 years. This model was used to plot VA change from the baseline to 10 years. The longitudinal VA over 10 years was also compared between ANZ and Swiss patients by using these models. A *P* value of 0.05 was considered statistically significant.

All analyses were conducted using R version 3.4.4 software (Vienna, Austria; http://www.R-project.org/), using the MGCV application (version 1.8-24) for generalized

TABLE 2. Outcomes in Eyes Completing 10 Years of Treatment

Outcomes Stratified by Regions	Australia and New Zealand	Switzerland
Completers	132 (28)	37 (12)
Patients	117	33
Mean ± SD baseline VA letters (logMAR) (Snellen equivalent)	60.7 ± 17 (20/60)	61.6 ± 14 (20/60)
Mean ± SD final VA letters (logMAR) (Snellen equivalent)	60.1 ± 20.7 (20/60)	46.8 ± 28.8 (20/125)
Mean change in VA letters (logMAR) (95% CI)	−0.9 (95% CI: −4.9 to 3.1)	−14.9 (95% CI: −24 to −5.7)
Proportion with ≥10-letter gain	34%	19%
Proportion with ≥10-letter loss	27%	49%
VA ≥70 letters (20/40 Snellen equivalent), baseline/final	36%/42%	24%/35%
VA ≤35 letters (20/200 Snellen equivalent), baseline/final	7%/14%	5%/38%
Proportion of active visits	38%	69%
Median injections (Q1, Q3)	53 (35, 69)	42 (17, 71)
Median visits (Q1, Q3)	66 (48, 80)	78 (60, 91)

CI = confidence interval; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; VA = visual acuity.
Values are n (%), mean ± SD, interquartile range, and %.

additive (mixed) model computation and the SURVIVAL application (version 2.38) for dropout analysis.[11–13]

RESULTS

A TOTAL OF 795 TREATMENT-NAÏVE EYES OF 690 PATIENTS starting treatment with a VEGF inhibitor between January1, 2006, and December 31, 2008, were identified in the FRB! project registry. The mean age of the patients at their first eye injection ("baseline") was 79.2 ± 7.4 years old, and the mean presenting VA was 53.8 ± 17.9 letters (20/80 Snellen equivalent). Table 1 shows the demographic characteristics of the eyes from the 2 regions. More than half of the eyes (58%) received treatment as monotherapy for the entire period: 411 eyes (52%) with ranibizumab and 51 eyes (6%) with bevacizumab. A total of 187 eyes (24%) exchanged between ranibizumab and bevacizumab, 1 eye (0.12%) between aflibercept and bevacizumab, 87 eyes (11%) between ranibizumab and aflibercept, and 58 eyes (7%) between all 3 anti-VEGF agents for the treatment of nAMD during the period.

• **OUTCOMES AT 10 YEARS:** Of the 795 eyes identified, 169 eyes (21%) of 150 patients completed 10 years of continuous treatment. The mean VA of these 169 eyes at baseline was 60.9 ± 16.4 letters (20/60 Snellen equivalent). The mean VA in eyes from ANZ had dropped by 0.9 letters at 10 years ($P = 0.7$), although there was a drop of 14.9 letters in eyes from Switzerland ($P < 0.001$) (Table 2). The proportion of eyes with VA of ≥70 letters (20/40) improved at 10 years in both regions (Table 2). The proportion of eyes with VA of ≤35 letters (20/200) increased in both regions at 10 years (Table 2).

Figure 1A illustrates the VA outcomes over 10 years in eyes of patients who continued nAMD treatment with VEGF inhibitors. The mean VA (95% confidence interval [CI]) in eyes from ANZ improved by 6.9 (95% CI, 4.8-9.1) letters from baseline in the first year of treatment. Mean (95% CI) visual acuity remained at least 5 letters above the baseline level for 5 years, decreasing to +3.7 (95% CI, 0.5-6.9) letters at the end of the sixth year; +3.2 (95% CI, −0.3 to 6.7) letters for the seventh year; +2.2 (95% CI, −1.5 to 5.8) letters for the eighth year; +0.6 (95% CI, −3.1 to 4.2) letters at the ninth year; and −0.9 (95% CI, −4.9 to 3.1) at the end of year 10 (Figure 1A). Eyes from Switzerland had an improvement in mean (95% CI) VA from the baseline only in the first year of treatment (2.6 [95% CI, −0.8 to 6]) letters (Figure 1A). The mean VA in the Swiss eyes dropped from the baseline level during the second year of treatment and thereafter up until 10 years when the mean VA was 14.9 (95% CI, −24, −5.7]) letters less than the baseline level.

Eyes were divided into 3 groups by baseline visual acuity to evaluate the effect of baseline VA on outcomes and treatment patterns. Patients with eyes with better initial vision were more likely to complete 10 years of treatment. The mean VA of eyes with good initial VA (≥70 letters [20/40]) deteriorated from the point at which treatment was started, whereas the mean VA of eyes with poor initial VA (≤35 letters [20/200]) improved, although the final mean VA in those eyes was still far worse than that of the group that started with good vision. Eyes from ANZ received a similar number of injections regardless of the VA at baseline, whereas eyes with poor initial VA in the Swiss cohort received far fewer injections than eyes with good initial vision.

Eyes in ANZ were treated more frequently than eyes from Switzerland from the start of treatment (Figure 1B).

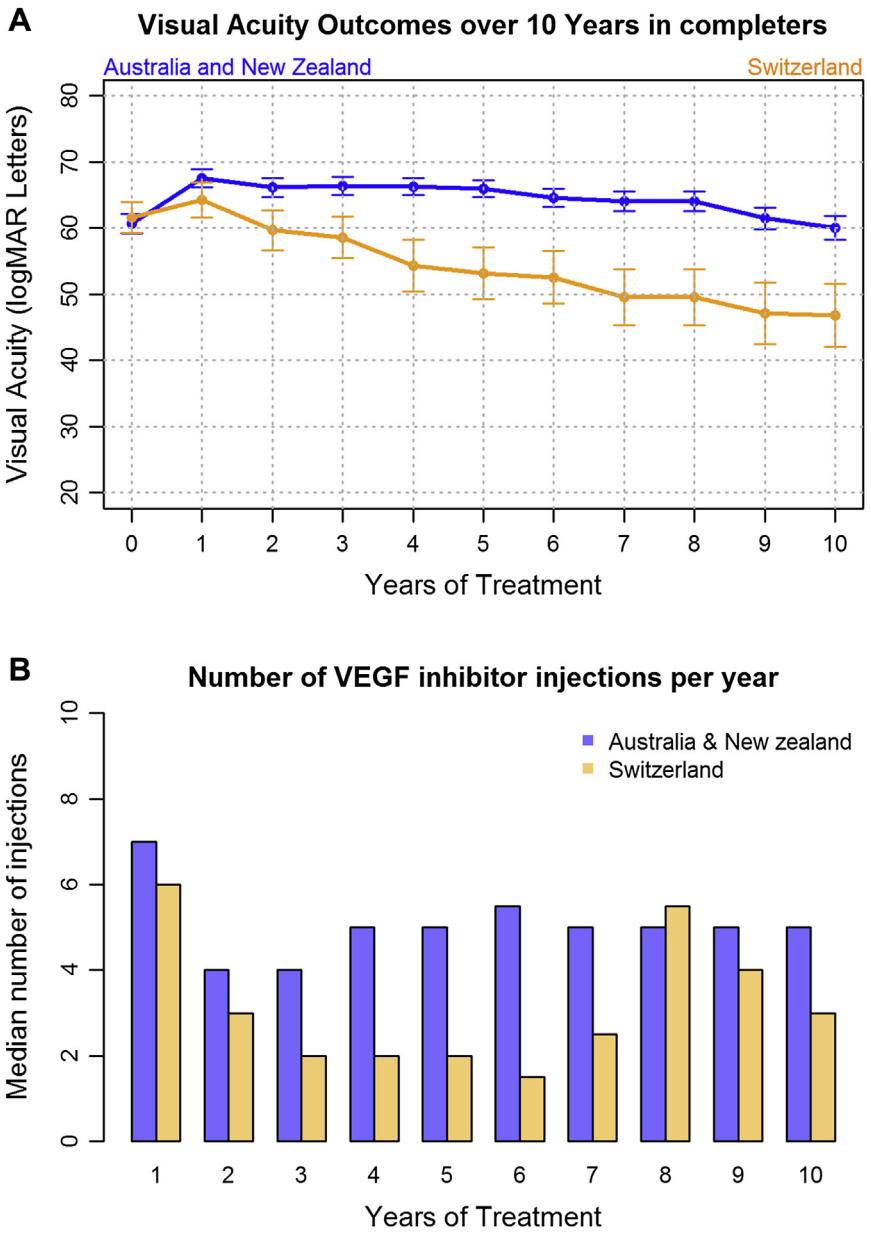

FIGURE 1. (A) Graph shows yearly mean visual acuity in eyes completing 10 years from the start of vascular endothelial growth factor (VEGF) inhibitor treatment for neovascular age-related macular degeneration (blue = Australia and New Zealand; orange = Switzerland). Error bars indicate ±1 SE. (B) Bar graph compares the median number VEGF inhibitor injections in the Australia and New Zealand and the Swiss cohorts. logMAR letters [Snellen equivalent] = 20 [20/400], 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], and 80 [20/25].

The median (Q1, Q3) number of injections in the first year was 7 (4, 8) and 6 (4, 7) in the ANZ cohort and in the Swiss cohort. Eyes in ANZ patients from 3-7 years received twice as many injections as eyes in the Swiss cohort (Figure 1B). The median (Q1, Q3) number of visits in ANZ was 8 (7, 10) in the first year, dropping to 5-6 per year thereafter. Eyes in Swiss patients had a median of 10 (9, 11) visits in the first year, dropping to 7 to 8 visits per year from the third year onward.

Treatment regimens can be inferred by injection and visit numbers. A treat-and-extend regimen aims to give the next anti-VEGF injection just before the lesion reactivates, whereas a pro re nata regimen treats the lesion only when it is active. Eyes in ANZ group received more injections over 10 years (median, 53 vs 42; $P < 0.001$) than those in Switzerland with fewer visits (median, 66 visits vs 78, respectively) (Table 2), indicating that eyes in ANZ received a treat-and-extend regimen, whereas eyes

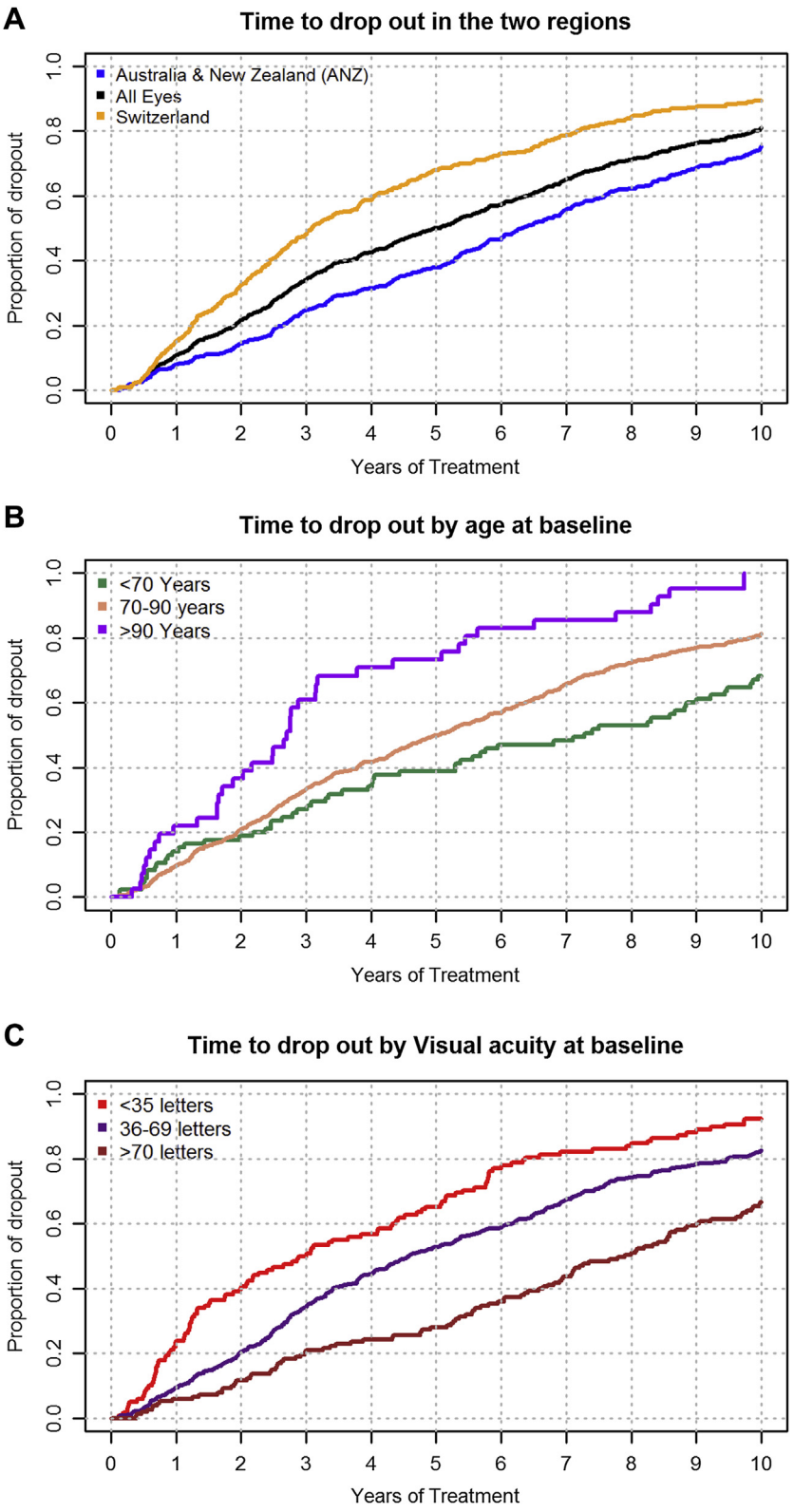

FIGURE 2. Kaplan-Meier plot for time to dropout from vascular endothelial growth factor inhibitor treatment in eyes with neovascular age-related macular degeneration according to region (A), age group (B), and visual acuity at baseline (C). logMAR letters [Snellen equivalent] = 20 [20/400], 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], 80 [20/25], respectively.

in Switzerland received a predominantly pro re nata treatment regimen (they might have been treated more intensively from year 8 onward). The proportion of visits over 10 years when the lesion was graded "active" was lower in ANZ (38%) than in Switzerland (69%) (Table 2), also consistent with a treat-and-extend regimen.

Fifty-four (32%) of the 167 eyes from both regions treated for 10 years lost ≥10 letters. The cause of ≥10 letters' loss after 10 years of treatment was assessed from 3 of the major contributing practices (which contributed 74% of the cases) based on clinical notes and optical coherence tomography images. Central macular atrophy was the most common cause in eyes from ANZ, accounting for 41% of the total, whereas it was reported in only 6% of the eyes in the Swiss cohort ($P = 0.01$). Subretinal fibrosis (fibrosis between neural retina and retinal pigment epithelium with or without macular atrophy) was the major cause in eyes from Switzerland (78%), whereas it was reported in 28% of eyes from ANZ ($P = 0.003$). Infectious endophthalmitis was the cause in 5% of the eyes from ANZ.

• **VISUAL OUTCOMES OF EYES NOT COMPLETING 10 YEARS:** A total of 626 eyes from 553 patients did not complete 10 years of continuous treatment. Just under 11% of eyes dropped out before they completed 1 year of treatment, and 79% had dropped out by 10 years (Figure 2A). More eyes from the Swiss cohort dropped out than from the ANZ cohort (Figure 2A). Eyes that dropped out were older (80 ± 7years vs 76 ± 8 years, respectively; $P < 0.001$) and had lower vision at baseline (mean VA 51.9 ± 17.7 letters [20/100 Snellen equivalent] vs 60.9 ± 16.4 letters [20/60 Snellen equivalent], respectively; $P < 0.001$) than those that completed 10 years of continuous treatment (Figure 2, B and C).

Figure 3, A and B illustrate the number of eyes in the 2 regions that dropped out over time and compares their mean VA from baseline to the last observation before they discontinued treatment. The reasons for treatment discontinuation were recorded in 477 (76%) of these eyes. The major reasons for treatment discontinuation were patient transferred to another doctor, 30% (ANZ, 41; Switzerland, 150) and death, 14% (ANZ, 51; Switzerland, 34). Successful treatment, 3% (ANZ, 15; Switzerland, 1) and medical contraindication, 1% (ANZ, 3; Switzerland, 3) were other reasons given that were unlikely to be related to poor outcomes. Reasons which could be related to a poor outcome (further treatment considered futile: 20% [ANZ, 70; Switzerland, 56], patient declined treatment: 9% [ANZ, 20; Switzerland, 36]) were reasons given for a significant minority.

Figure 4 shows the predicted VA outcome over 10 years in eyes treated with VEGF inhibitor injections for nAMD using VA outcomes of all eyes that started treatment 10 years previously, regardless of the duration of follow-up. The predicted mean VA in eyes from ANZ improved from baseline during the first 4 years (mean [95% CI] gain in VA; 4.7

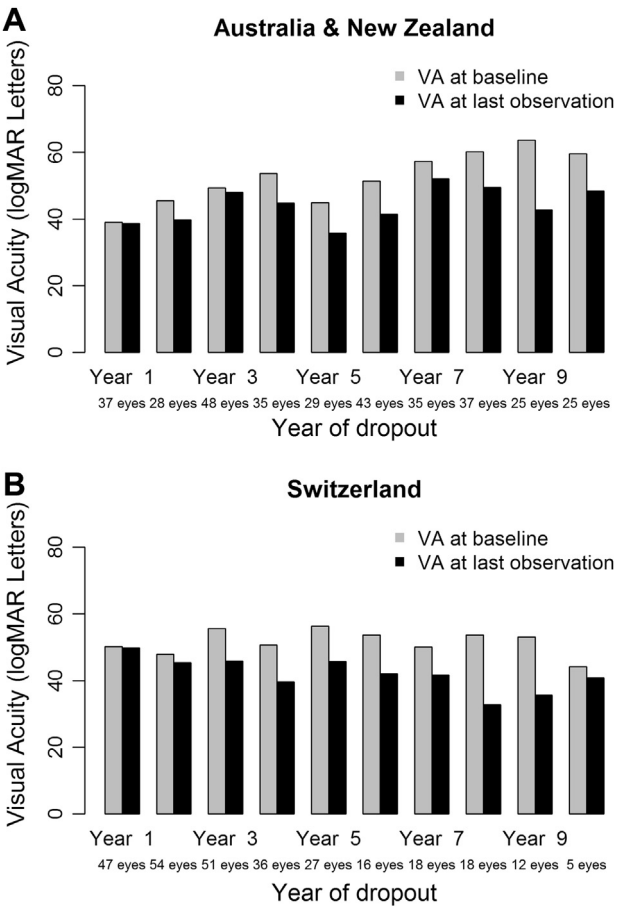

FIGURE 3. Comparison of the mean visual acuity (VA) at baseline (gray bars) with the last observed mean VA (black bar) in eyes of patients who dropped out from Australia and New Zealand (A) and Switzerland (B). "n" represents the number of eyes with the last observation in that year. logMAR letters [Snellen equivalent] = 20 [20/400], 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], 80 [20/25].

letters [95% CI, 3.6-5.9] in year 1; 2.4 letters [95% CI, 1.2-3.4] in year 2; 0.9 [95% CI, −0.3 to 2.1] letters in year 3; and 0.5 [95% CI, −0.5 to 1.5] letters in year 4), but from the fifth year onward, it dropped below the baseline level; and at 10 years, the predicted mean VA change was −5.3 (95% CI, −6.5 to −4.1) letters (Figure 4). Eyes from Switzerland had an improvement in the predicted mean VA from the baseline only in the first year of treatment (1.1 letters [95% CI, 0.0-2.3]) (Figure 4). The predicted mean VA in those eyes dropped below the baseline level from the second year onward, and at 10 years the predicted mean VA change was −14.7 (95% CI, −15.8 to −13.5) letters. The ANZ cohort had better visual acuity over the entire 10-year treatment period ($P < 0.001$) (Figure 4).

• **ADVERSE EVENTS:** A total of 18,920 intravitreal injections were administered in the 795 eyes during the 10-year period. The rate of adverse events per injection

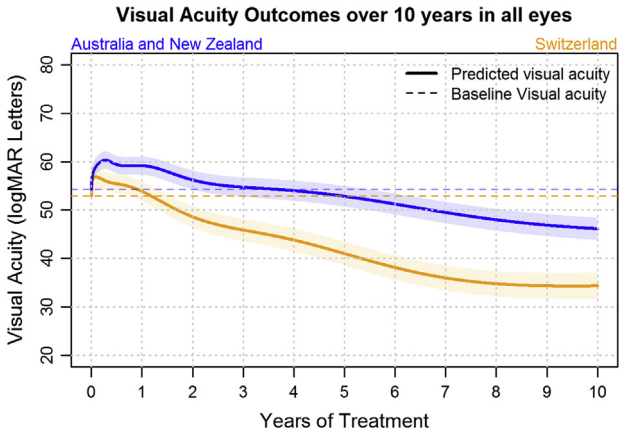

FIGURE 4. Predicted visual acuity over 10 years in eyes (blue = Australia and New Zealand; orange = Switzerland) treated with vascular endothelial growth factor inhibitors. Predictions were made from a longitudinal generalized additive model using visual acuity in both completers and noncompleters. Shaded zone on each line represents the confidence interval. logMAR letters [Snellen equivalent] = 20 [20/400], 30 [20/250], 40 [20/160], 50 [20/100], 60 [20/63], 70 [20/40], 80 [20/25].

was low (0.4%). The rate of infectious endophthalmitis, the most serious adverse event associated with intraocular injections, was 0.02% per injection.

DISCUSSION

THIS STUDY PROVIDES THE FIRST 10-YEAR EVIDENCE FOR THE efficacy of VEGF inhibitors for neovascular AMD in real-world practice. A total of 795 eyes were identified with nAMD from ANZ and Switzerland starting treatment with VEGF inhibitors at least 10 years earlier. The VA outcome of the 132 eyes (28%) from ANZ that completed 10 years of continuous treatment was reasonably good, with a mean loss of just 0.9 letters and better than that of the 37 eyes (12%) from Switzerland that lost a mean of 14.9 letters. Eyes from Switzerland generally received fewer treatments than eyes from ANZ and were more likely to have active disease when they were assessed.

Better outcomes in the ANZ cohort were likely due to higher injection rates during the maintenance phase of treatment and the fact that the disease was better controlled as a result of being treated more intensively. Both groups had similar mean VA at the start of treatment, but the group from Switzerland lost 14 letters more than the ANZ group over 10 years. A previous study from the FRB! registry reported that eyes in Australia and New Zealand received more treatments for nAMD and that the outcomes were better than those reported by a similar study in the United Kingdom.[14,15] Injections of eyes at 80% of visits, as was the case here for the ANZ cohort, reflects a treat-and-extend regimen, which is widely used in ANZ, whereas injections at 60% of visits, which was found in the Swiss cohort, indicate a pro re nata regimen (i.e., treated only when the lesion was active).[14] Data suggest that treat-and-extend may provide better VA outcomes and better disease control with more injections at fewer visits. Other potential causes of regional variations in treatment outcomes may be barriers to access to the drug and the capacity of the regional health care system to provide sufficient injections. The Swiss cohort received more injections from 8 years onward, consistent with a shift from a pro re nata regimen to a treat-and-extend regimen.

Baseline visual acuity had a significant effect on outcomes and treatment patterns. More eyes with VA of ≥70 letters (20/40) at presentation completed 10 years of continuous treatment. These eyes lost vision from the baseline on average but still had relatively good vision at 10 years, in contrast to eyes with worse starting vision, which had better improvements, or less loss, in VA compared to baseline but still had inferior final VA.

Subretinal fibrosis and macular atrophy were the common causes for loss of VA ≥10 letters during the 10-year period. More eyes in the Swiss cohort (78%), which generally received fewer injections and were more active, lost ≥10 letters over 10 years due to subretinal fibrosis, which is usually accompanied by macular atrophy. Macular atrophy without fibrosis (41%) was more common in the ANZ cohort, which received more injections and was generally less active. These are likely underestimates of the actual long-term risk of developing subretinal fibrosis and macular atrophy, as some eyes that developed these complications may have discontinued treatment early. Macular atrophy and subretinal fibrosis did not, however, develop universally as previously feared.[6] It cannot be determined from the data whether macular atrophy was caused or exacerbated by treatment with VEGF inhibitors or whether it is simply the natural history of the underlying condition.

Long-term observational studies in elderly populations inevitably have high drop-out rates.[16] The Comparison of Age-Related Macular Degeneration Treatment Trials study at 5 years assessed VA in 647/1208 (54%) patients initially enrolled.[17–19] The Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials study reported 7-year outcomes of ranibizumab treatment in 65 of the 357 (18%) subjects that were enrolled in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) clinical trials.[6] Approximately 11% of the eyes dropped out in the present study within the first year of treatment, increasing to 79% (including deaths) at 10 years. The data presented here are of limited value in advising patients what will happen 10 years after starting treatment, which is practically impossible to do anyway,

but they do show what may be achieved in many eyes with adequate treatment. There was an estimated loss in mean visual acuity of just 1 line at 10 years when all eyes, completers, and dropouts, were included in ANZ, where eyes were treated more intensively.

Eyes that discontinue treatment for any reason should be taken into account when analyzing outcome data from the real-world clinical practice. The mean VA of the eyes that dropped out tended to fall below the baseline at the time treatment had discontinued, suggesting that only eyes that had a good result remained under active treatment. This is a weakness of all observational studies, but it would not account for the differences in outcomes from the two regions that we describe. Of the 477 eyes where reasons for treatment discontinuation were recorded, 28% were for reasons that were likely to be related to a poor outcome, such as patient declines or further treatment considered futile. The commonest reason, going to another doctor (30%), could be due to simple convenience or perhaps the patient was looking for a better outcome.

There are currently no published 10-year data for the treatment of nAMD with VEGF inhibitors with which to compare the present results. Haddad and associates[7] reported that 54 eyes followed for 8 years in France with a mean of 28 injections of VEGF inhibitors lost 5.5 letters. The Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials study reported a mean loss of 8.6 letters in 65 eyes followed for 7 years, with only 23% achieving VA of ≥70 letters.[6] Those eyes received only a mean of 6.8 injections of VEGF inhibitors during the mean 3.4-year interval from the end of the pivotal phase III studies they had participated in and the end of the study period. A subgroup that received >11 injections during this period had significantly better mean gains in vision. This is consistent with the apparent association found in the present study of improved outcomes with higher injection rates and better disease control. Peden and associates[8] reported a large mean (12.1 letters) visual improvement in 44 eyes that had received an average of 10.5 injections per year for at least 7 years with 43% achieving VA of ≥70 letters. The baseline VA of eyes in the study by Peden and associates,[8] however, had far greater potential for improvement because their mean baseline VA was 15 letters lower than that of eyes in the present study, which received roughly half the treatment burden and had a better 10-year outcome. Although the ideal treatment requirement for nAMD has yet to be determined, our data suggest that a service increasing its median annual number of injections from 4 to 5 would provide better control of the lesion activity and improve the long-term outcomes for its patients.

This study has several limitations which are inherent in observational data. Treatment decisions in routine clinical practices were made without adjudication by a reference center or according to study protocols, as is the case in clinical trials. Case selection and treatment regimen may also differ among treating physicians. Dropout rates were high, but this is unlikely to have affected the regional variation in the observed outcomes. The major strength of this study is that it reports treatment outcomes in eyes starting VEGF inhibitor injections for nAMD at least 10 years earlier in real-world clinical practice. The VA outcomes at the last observation in the eyes that dropped out before 10 years and the reasons for treatment discontinuation are also described.

Overall, better VA outcomes were found in the region where eyes with nAMD were treated with more injections of VEGF inhibitors, using a treat-and-extend regimen. Importantly, it was found that macular atrophy does not develop universally in eyes receiving long-term treatment with VEGF inhibitors. Eyes presenting with better VA, which were presumably diagnosed earlier, tended to receive treatment for longer and end up with better vision. In contrast to the natural history of nAMD, which is progression to severe loss of vision,[20] this study found that satisfactory outcomes could be achieved in many eyes, particularly if they received an adequate number of injections.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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