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# Accepted Manuscript

Projection of long-term visual acuity outcomes based on initial treatment response in neovascular age-related macular degeneration

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1     **Projection of long-term visual acuity outcomes based on initial treatment response in**  
2                     **neovascular age-related macular degeneration**

3

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32 **Abstract**

33 **Purpose:** To explore various methods for assessing the early response to vascular endothelial  
34 growth factor (VEGF) inhibitors for neovascular age-related macular degeneration and  
35 investigate their association with 3 year visual acuity (VA) outcomes.

36 **Design:** Observational study from a prospectively collected registry.

37 **Participants:** Treatment-naïve eyes in the Fight Retinal Blindness! outcomes registry that  
38 commenced anti-VEGF therapy between 1st January 2007 and 1st March 2014 that received  
39 3 anti-VEGF injections within the first 3 months.

40 **Methods:** The early response was defined as occurring up until the 4th injection. Various  
41 early response metrics, which included both continuous and categorical variables, were  
42 explored: 1) achieving good VA ( $\geq 70$  letters [20/40]), 2) absolute change in VA from  
43 baseline, 3) time to first grading of the choroidal neovascular lesion as inactive, 4) maximum  
44 rate of VA change between successive injections.

45 **Main Outcome Measures:** Proportion of eyes achieving  $\geq 70$  letters at 3 years.

46 **Results:** This study included 2051 treatment-naïve eyes from 1828 patients. Achieving good  
47 vision at 3 years was significantly associated with 1) having good vision by the 4th injection  
48 (odds ratio [95% CI]: 9.8 [6.5, 14.7] for  $VA \geq 70$  vs.  $VA < 70$  letters), 2) small (1-5 letters) or  
49 large ( $> 5$  letters) early VA gains (1.8 [1.2, 2.6],  $P = 0.002$  and 1.8 [1.3, 2.5],  $P < 0.001$  vs.  
50 eyes with early VA loss), 3) fewer injections until first grading of lesion inactivity (1.6 [1.2,  
51 2.1],  $P < 0.001$  for  $\leq 3$  vs.  $> 3$  injections), 4) gradual change (between -4 and 4 letters) or rapid  
52 ( $> 5$  letters) gains between successive injections (1.7 [1.1, 2.6],  $P = 0.015$  and 1.6 [1.1, 2.3],  $P$   
53 = 0.018 for gradual change and rapid gain vs. rapid loss). Eyes that achieved small or large  
54 early gains achieved similar vision at 3 years (65.0 and 64.7 letters respectively), and had  
55 better vision than eyes with early VA loss (57.2 letters).

56 **Conclusions:** Attainment of good vision by the 4th injection was strongly associated with 3  
57 year visual outcomes, while other early response parameters had a moderate association. The  
58 early response during the initial 3 monthly loading doses can be a useful guide for subsequent  
59 treatment decisions.

60

## 61 **Introduction**

62 Large variations in the response to vascular endothelial growth factor (VEGF) inhibitors in  
63 patients with neovascular age-related macular degeneration (nAMD), as reported in clinical  
64 and observational studies, have been attributed to a number of factors, notably demographic  
65 and clinical characteristics at baseline and treatment protocols.<sup>1-7</sup> Baseline clinical  
66 characteristics such as age, lesion size and lesion subtype in particular have been identified in  
67 multiple studies as predictive of visual outcomes.<sup>1, 2, 8, 9</sup> In addition, several studies have  
68 assessed the effect of genetic factors on treatment outcomes, but these associations are  
69 weaker or non-existent.<sup>4, 10-12</sup> By contrast, the visual acuity (VA) at presentation is one of the  
70 strongest predictors of long-term outcomes, whereby eyes with poor starting VA are more  
71 likely to achieve larger gains in vision, but have worse final vision than those that present  
72 with good VA.<sup>4, 5, 8</sup>

73 While VEGF inhibitors have generally been shown to provide good visual outcomes for  
74 nAMD, some eyes do not respond well to treatment.<sup>5</sup> Predictive markers based on an eye's  
75 early response to treatment may assist in making subsequent treatment decisions and guiding  
76 patient expectations. A post-hoc analysis of the Comparison of AMD Treatments (CATT)  
77 cohort identified the 12 week change in VA to provide significantly more predictive power  
78 for 2 year outcomes compared with the baseline and 4 week response.<sup>13</sup> In the present study,  
79 we explored various metrics for measuring the early response to treatment with VEGF  
80 inhibitors, and assessed their ability to predict 3 year visual outcomes. We also assessed  
81 whether these early response markers provided additional predictive power that could not  
82 already be inferred from the baseline vision.

83

## 84 **Methods**

85 This study followed the STROBE checklist items for reporting observational study data.<sup>14</sup>

86

### 87 *Study Design*

88 Observational study using data from a prospectively collected registry.

89

90 *Setting*

91 Data were obtained from the Fight Retinal Blindness! (FRB!) database, a large international  
92 registry that tracks real-world outcomes of treatment of nAMD. The FRB! database is  
93 compliant with the International Consortium for Healthcare Outcome Measurement's  
94 (ICHOM) minimum standard set of treatment outcomes for macular degeneration.<sup>15</sup> Further  
95 details of the FRB! database have been published elsewhere.<sup>16</sup> Ethics approval was obtained  
96 from the Human Research Ethics Committees of the Royal Victorian Eye and Ear Hospital,  
97 the Royal Australian and New Zealand College of Ophthalmologists, the University of  
98 Sydney and the Cantonal Ethics Committee Zurich, Switzerland. This study conformed to the  
99 tenets of the Declaration of Helsinki.

100

101 *Data Sources/Measurements*

102 The FRB! system collects data from each clinical visit, including the number of letters read  
103 on a logarithm of the minimum angle of resolution (LogMAR) VA Chart (best of  
104 uncorrected, corrected or pinhole), treatment given, choroidal neovascular (CNV) lesion  
105 activity, as judged by the treating physician based on funduscopy, optical coherence  
106 tomography imaging or fluorescein angiography alone or in combination (an active grading  
107 indicated the presence of "intraretinal or subretinal fluid attributable to leak from choroidal  
108 neovascularisation lesion or fresh haemorrhage"), and ocular adverse events. Previous  
109 treatments received, lesion subtype as determined by the practitioner based on retinal  
110 angiography and lesion size (greatest linear dimension, GLD) were recorded during the  
111 baseline visit. Treatment decisions, including drug choice and treatment frequency, were at  
112 the discretion of the practitioner in consultation with the patient, thereby reflecting real-world  
113 practice.

114 We explored several avenues for assessing the early response. Most protocols for treating  
115 nAMD generally start with a loading of 3 injections of a VEGF inhibitor at monthly intervals  
116 regardless of the treatment regimen.<sup>17, 18</sup> Thus, the early response was specified to occur at  
117 the time the 4th injection was due. The metrics for measuring the early response and the  
118 expected relationship with long-term outcomes are described below:

- 119 1. **Achieving good vision**, defined as having  $\geq 70$  letters (20/40 vision)
- 120 2. **Absolute change in VA from baseline**, defined as the change in VA from baseline,  
121 was analysed as a continuous variable and as a categorical variable based on the  
122 following groups:
- 123 1. *Early Loss*:  $\leq 0$  letter improvement i.e. loss of vision or no change in vision
  - 124 2. *Small Early Gain*: 1-5 letter improvement
  - 125 3. *Large Early Gain*:  $> 5$  letter improvement
- 126 3. **Time to CNV Inactivity**, defined by the lesion activity status. Following the  
127 definitions from a previous FRB! study,<sup>19</sup> we defined the following groups:
- 128 1. *Short Induction*: Eye required  $\leq 3$  injections until the first grading of the CNV  
129 lesion as inactive
  - 130 2. *Long Induction*: Eye required  $> 3$  injections before the lesion was graded as  
131 inactive. This included eyes whose CNV lesion remained active throughout the 3  
132 year study period.
- 133 4. **Maximum rate of VA change**, defined as the highest rate of change in VA between  
134 two successive injections until the 4th injection was due and converted to a  
135 standardised rate of letter change per 4 weeks. This rate of change was analysed as a  
136 continuous variable and as a categorical variable based on the following groups:
- 137 1. *Rapid Loss*: Largest VA change between successive injections  $> 5$  letter loss per 4  
138 weeks
  - 139 2. *Gradual Change*: Largest VA change between successive injections between -4  
140 and 4 letters per 4 weeks
  - 141 3. *Rapid Gain*: Maximum of  $\geq 5$  letter improvement per 4 weeks.
- 142

### 143 **Participants**

144 Treatment-naïve eyes with nAMD tracked by the FRB! registry commencing anti-VEGF  
145 therapy between 1st January 2007 and 1st March 2014 were considered, thereby allowing all  
146 eyes the possibility of completing at least 3 years of follow-up at the time the analysis was  
147 conducted. For inclusion, eyes were also required to have received 3 monthly anti-VEGF  
148 injections as a loading dose to establish the early response and limit the possibility that poor  
149 early response was due to under-treatment. Completers were defined as eyes completing 3



150 years of follow-up while non-completers were eyes that did not complete 3 years of follow-  
151 up.

### 152 *Outcome Measures*

153 The primary outcome was the proportion of eyes achieving VA $\geq$ 70 letters at 3 years.

154 Secondary outcomes included the change in VA at 3 years and non-completion rates.

155

### 156 *Statistical Analysis*

157 Descriptive data included the mean, standard deviation (SD), median, 25th and 75th

158 percentiles (Q1, Q3), and percentages where appropriate. Baseline demographics were

159 compared using ANOVA, Kruskal-Wallis, t-test, Wilcoxon rank sum and Chi-square tests.

160 Longitudinal generalised additive models were used to plot longitudinal visual outcomes over

161 3 years of treatment and included data from completers and non-completers.<sup>20, 21</sup>

162 The early response was analysed according to the 4 definitions described above. Logistic

163 regression models were also performed with the VA at 3 years as a categorical variable (<70

164 letters vs.  $\geq$ 70 letters) and odds ratios reported. Linear mixed-effects models were used to

165 assess the relationship between the change in VA and final VA at 3 years and early response

166 definitions. Since these early responses were likely to be correlated, separate models were fit

167 for each definition. Injection frequency was analysed using Poisson regression models with

168 an offset for log follow-up duration (days). Cox-proportional hazards models were used to

169 assess non-completion rates and visualised using Kaplan-Meier survival curves.

170 Covariates for linear, Poisson and Cox-proportional hazards models also included

171 adjustments for age, lesion size, lesion type (fixed-effects) and clustering by practice and

172 patient (random-effects).

173 Baseline VA was not included as a covariate to avoid potential multicollinearity with the

174 early responses. Instead, separate models were fitted with baseline VA instead of the early

175 response to determine whether using the early response is better than simply using the

176 baseline VA for predicting outcomes. Models were compared using marginal R<sup>2</sup> values for

177 mixed-models.<sup>22</sup> We also report Akaike's Information Criterion (AIC) for model comparison

178 where smaller values indicate better fit. Sensitivity analyses were conducted in which only

179 one eye per patient was analysed for bilateral patients; either the first presenting eye or the  
180 worse presenting eye if both eyes were diagnosed simultaneously.

181 Pairwise comparisons were performed using the Holm-Bonferroni adjustment where  
182 appropriate. A p-value of 0.05 was considered statistically significant.

183 All analyses were conducted in R version 3.3.2 using the *lme4* package (V1.1-13) for mixed-  
184 effects models and *coxme* package (V2.2-5) for Cox-proportional hazards models.<sup>23-25</sup>

185

## 186 **Results**

### 187 *Study Population*

188 This study included 2051 treatment-naïve eyes from 1828 patients (223 bilateral patients) that  
189 initiated treatment between 1st January 2007 and 1st March 2014. There were 762 (37%)  
190 eyes that did not complete 3 years of follow-up during the study period. The median (Q1,  
191 Q3) days until the 4th injection was 105 (91, 123) days. Baseline demographic characteristics  
192 partitioned by the categorical early response definitions set out above are summarised in  
193 Table 1.

194 Overall, there were 572 (28%) eyes with good VA ( $\geq 70$  letters, Snellen equivalent 20/40) at  
195 baseline; at the 4th injection this number had increased to 882 (43%) eyes. Approximately  
196 half of eyes underwent a longer period of monthly injections after the initial 3 loading  
197 injections (1067 eyes; 52%), including 222 eyes who either remained active by the end of the  
198 3 year follow-up (69 eyes) or at time of non-completion (153 eyes).

199 Eyes in the Large Early Gain group had significantly lower mean [SD] baseline VA (49.6  
200 [18.1] letters) compared with the Early Loss (60.1 [19.1] letters,  $P < 0.001$ ) and the Small  
201 Early Gain (63.1 [14.4] letters,  $P < 0.001$ ) groups. However, we note that eyes in the Early  
202 Loss group had similar baseline VA to the Small Early Gain group ( $P = 0.13$ ). Lesion sizes  
203 were significantly smaller in eyes with good VA at 4th injection (median [Q1, Q3]: 1934 $\mu\text{m}$   
204 [1124, 2800] vs. 2500 $\mu\text{m}$  [1500, 3500],  $P < 0.001$ ) and in eyes with shorter time to inactivity  
205 (median [Q1, Q3]: 2000 [1298, 3000]  $\mu\text{m}$  vs. 2500 [1500, 3500]  $\mu\text{m}$ ,  $P < 0.001$ ).

206 The overall mean (SD) early change in VA was 6.1 (13.2) letters; the overall mean (SD)  
207 maximal change in VA between successive injections was 5.2 (14.6) letters.

208

### 209 *Achieving Good Vision at 3 Years*

210 The association between categorical early response definitions and achieving good vision  
211 ( $\geq 70$  letters, 20/40) at 3 years is summarised in Table 2. Of the 1289 eyes that completed 3  
212 years of treatment, 608 (47%) had good VA after 3 years of treatment. Overall, achieving  
213 good VA by the 4th injection was the best predictor of good vision at 3 years ( $R^2 = 0.30$ ),  
214 outperforming the model using baseline VA ( $R^2 = 0.17$ ).

215 Eyes were significantly more likely to achieve good VA (odds ratio [95%CI]) if they had  
216 already achieved good vision by the 4th injection (9.8 [6.5, 14.7],  $P < 0.001$  for  $VA \geq 70$  vs.  
217  $VA < 70$  letters by 4th injection), achieved small early or large early gains (1.8 [1.2, 2.6],  $P =$   
218 0.002 and 1.8 [1.3, 2.5],  $P < 0.001$  for small and large early gains vs. early loss), had a short  
219 induction (1.6 [1.2, 2.1],  $P < 0.001$  for short vs. long induction), or experienced gradual  
220 change or rapid gain (1.7 [1.1, 2.6],  $P = 0.015$  and 1.6 [1.0, 2.3],  $P = 0.018$  for gradual  
221 change and rapid gain vs. rapid loss). However, with the exception of achieving good vision  
222 by the 4th injection, the remaining early response definitions failed to outperform the baseline  
223 model. Sensitivity analyses including only one eye per patient yielded the same result  
224 (supplementary material S1).

225 Approximately three quarters (73.0%) of eyes with good VA at the 4th injection maintained  
226 good vision after 3 years of treatment. Encouragingly, an additional 149/1289 (22.6%) eyes  
227 that had  $< 70$  letters at the 4th injection achieved  $> 70$  letters at year 3.

228

### 229 *Visual Acuity Outcomes at 3 Years*

230 The association between early response definitions and change in VA at 3 years is  
231 summarised in Table 3. Longitudinal VA outcomes through 3 years for categorical early  
232 response variables are shown in Figure 1. Overall, the model using the absolute change in VA  
233 at the 4th injection (continuous variable) provided the best fit ( $R^2 = 0.37$ ) for predicting the

234 long-term change in VA, outperforming the model using baseline vision instead of the early  
235 response ( $R^2 = 0.20$ ).

236 Eyes in the Early Loss group at the 4th injection had worse vision (mean VA change [95%  
237 CI]) at 3 years (-5.9 [-7.5, -4.3] letters) than the Small Early Gain (0.7 [-0.9, 2.3] letters,  $P <$   
238 0.001) and Large Early Gain groups (12.8 [11.4, 14.1],  $P < 0.001$ ). Applying these same  
239 categories for VA change at 3 years (Figure 2), 68% of eyes that experienced Early Loss had  
240 VA loss at the end of the third year of treatment; these eyes had a relatively high (mean [SD])  
241 baseline VA (64.4 [16.2]). The remaining eyes with Early Loss went on to achieve a small  
242 (14%) or large (18%) gain in vision despite this early loss, possibly indicating a delayed  
243 response. Similarly, 71% of eyes in the Large Early Gain group maintained their large VA  
244 gain at 3 years. Only 20% of eyes in the Small Early Gain group had a 1-5 letter gain at 3  
245 years, with the remaining 80% split evenly between VA loss and large gains.

246 Visual acuity at 3 years (mean VA [SD]) was significantly worse for eyes in the Early Loss  
247 group (57.4 [20.7]) than the Small Early Gain (65.0 [17.2],  $P < 0.001$ ) and Large Early Gain  
248 groups (64.7 [17.6],  $P < 0.001$ ). Eyes in the Large Early Gain group had a significantly  
249 greater improvement in vision at 3 years compared with the Small Early Gain group ( $P <$   
250 0.001) although the VA at 3 years was similar for these 2 groups ( $P = 0.826$ ).

251 When eyes were grouped by early maximal rate of VA change, similar patterns were  
252 observed whereby the Rapid Loss, Gradual Change, and Rapid Gain groups performed  
253 similarly to the Early Loss, Small Early Gain and Large Early Gain groups respectively  
254 (Table 3).

255 Eyes with shorter induction had significantly better VA (mean [SD]) at the end of 3 years  
256 (65.3 [17.9] letters vs. 59.6 [20.3] letters,  $P < 0.001$ ) although there was no significant  
257 difference in VA change ( $P = 0.145$ ).

258

### 259 ***Injection Frequency***

260 Overall, eyes completing 3 years of follow-up received a median (Q1, Q3) of 19 (15, 23)  
261 injections. More frequent injections were associated with higher VA change at 3 years (model  
262 coefficient [95%CI]: 0.31 [0.18, 0.44] letters at 3 years per injection,  $P < 0.001$ ). We did not

263 find an association between VA change at the 4th injection (continuous:  $P = 0.750$  and  
264 categorical:  $P = 0.754$ ) or maximum change of VA (continuous:  $P = 0.088$  and categorical:  $P$   
265  $= 0.345$ ) with the number of injections.

266

### 267 *Non-completion*

268 Change in VA at time of dropout, non-completion rates and their association with the early  
269 response are summarised in Table 4. Overall, 762 (37%) eyes did not complete 3 years of  
270 follow-up during the study period. Doctor-reported reasons for non-completion were  
271 available for 311 eyes and included patient going to another doctor (100 eyes [32%]), further  
272 treatment futile (79 eyes [25%]), patient deceased (57 eyes [19%]), patient declined further  
273 treatment (44 eyes [14%]), treatment successful (26 eyes [8%]) and medically contraindicated  
274 (5 eyes [2%]).

275 Visual outcomes were generally worse compared with completers, although early response  
276 groups followed similar trends. At last visit, higher VA (mean [SD]) was observed in eyes  
277 with  $VA \geq 70$  letters at the 4th injection (72.1 [13.4] vs. 43.0 [23.0] letters), small or large  
278 early VA gains (59.0 [23.4] and 55.6 [22.3] vs. 46.1 [26.2] letters for small and large early  
279 gains vs. early loss), short induction (56.0 [24.0] vs. 50.0 [24.7] letters for short vs. long  
280 induction) and gradual VA change or rapid VA gains (55.2 [25.3] and 54.3 [23.1] vs. 44.2  
281 [25.4] letters for gradual change and rapid gain vs. rapid loss). As with completers, 75% of  
282 eyes achieving good vision at the 4th injection retained good vision at time of last  
283 observation.

284 Survival curves for non-completion over time by early response group are presented in Figure  
285 3. Risk of non-completion (hazards ratio, HR [95% CI]) was significantly reduced when VA  
286 was  $\geq 70$  letters at the 4th injection (0.6 [0.5, 0.7] for  $VA \geq 70$  vs.  $VA < 70$  at the 4th injection,  $P$   
287  $< 0.001$ ), VA gains at the 4th injection were greater (0.8 [0.6, 0.9],  $P = 0.018$ , and 0.9 [0.7,  
288 1.0],  $P = 0.100$ , for Small and Large Early Gain vs. Early Loss; global test,  $P = 0.016$ ).

289

### 290 **Discussion**

291 This study explored several metrics for describing the early response to anti-VEGF treatment  
292 for nAMD and their ability to predict 3-year outcomes. We studied whether these early  
293 response definitions might predict long-term visual acuity outcomes better than the baseline  
294 visual acuity.

295 Eyes with  $VA \geq 70$  letters (Snellen equivalent of 20/40) at the time of the 4th injection were  
296 almost 10 times more likely have good vision at 3 years than eyes with  $VA < 70$  letters at the  
297 4th injection. Furthermore, although baseline vision was also a strong predictor of good  
298 visual acuity at 3 years, this relationship was not as strong as the visual acuity at the 4th  
299 injection.

300 Eyes that experienced early VA loss or small gain in the present study had somewhat similar  
301 baseline VA (60.1 and 63.1 letters respectively) but different outcomes at the 4th injection  
302 and at 3 years. Similar observations have been reported previously in DME for early  
303 moderate (5-9 letter gain) and suboptimal ( $< 5$  letter gain) VA gain groups.<sup>26</sup> Eyes that lost  
304 vision by the 4th injection had a mean loss of 1 line of vision at 3 years. For eyes that did not  
305 complete 3 years of treatment, there was a loss of almost 2 lines at time of dropout. In  
306 contrast, eyes that experienced a small early VA gain finished with the same visual acuity as  
307 eyes that achieved large early visual acuity gains (65.0 and 64.7 letters respectively) and were  
308 similarly likely to achieve good vision at 3 years. In addition, 18% of eyes that experienced  
309 early VA loss went on to gain more than 1 line of vision at 3 years, indicating a delayed  
310 response to anti-VEGF treatment. A post-hoc analysis of the CATT cohort reported 27% of  
311 eyes showing a loss of  $\geq 1$  line at 12 weeks went on to gain  $\geq 1$  line at 2 years.<sup>13</sup> Thus, it may  
312 be prudent to persist with anti-VEGF treatment even if the early response is poor in the  
313 absence of effective alternative treatments.

314 Measuring the maximum rate of VA change between successive injections was a novel way  
315 to assess the early response. We observed that approximately three quarters of eyes either  
316 gained (54%) or lost (18%) more than 5 letters at least once between 2 successive injections,  
317 with only 28% experiencing more gradual changes between successive injections. However,  
318 the maximal rate of change and raw early VA change definitions provided somewhat similar  
319 information, and the models using early VA change provided a better fit than the maximal  
320 rate of change.

321 Lesion activity, or shorter time to lesion inactivation, may be another useful marker of early  
322 treatment response. Eyes with a shorter time to lesion inactivity (3 or fewer injections) had  
323 better vision than eyes requiring more than 3 injections, both at baseline (57.8 vs 53.9 letters  
324 respectively) and at 3 years (65.3 vs. 59.6 letters respectively). They were also more likely to  
325 have good vision (70 letters, 20/40) at 3 years although the change in VA at 3 years was not  
326 significantly different ( $P = 0.091$ ). A previous analysis of 12-month outcomes found eyes  
327 with highly active lesions performed similarly to those with less active lesions,<sup>27</sup> however a  
328 longer term analysis is warranted to clarify the relationship between highly active lesions and  
329 visual outcomes.

330 We found that improvement in visual acuity up to the 4th injection of VEGF inhibitors was  
331 the most robust clinical predictor of visual acuity 3 years after starting treatment. Previous  
332 studies have also found greater predictive power between the 12 week change in VA with the  
333 1 and 2 year outcomes compared with only using the baseline VA.<sup>13</sup> This is probably because  
334 the disease is still largely VEGF-driven in these cases with a good early response. Cases  
335 which do not respond so well may be also be driven by other, less reversible, pathological  
336 processes such as inflammation, fibrosis and macular atrophy.<sup>13</sup>

337 The present study has some limitations. Treatment schedules after the initial loading phase,  
338 which might have influenced long-term outcomes,<sup>17,28</sup> were at the discretion of the physician  
339 and patient although most of the FRB! database practitioners use a treat and extend  
340 regimen.<sup>29,30</sup> It is however possible that patients with inferior initial responses may have  
341 subsequently been less compliant or extended out by the physician and suffered inferior  
342 outcomes as a result. Eyes with good VA at the 4th injection, tended to have better 3-year  
343 outcomes, and also on average, received more injections. Overall, more injections are  
344 associated with better visual acuity outcomes.<sup>29</sup> Still, eyes that were continued on monthly  
345 injections after the 3 initial monthly injections due to persistent activity – and thus had a high  
346 total number of injections - had worse outcomes at 3 years, possibly because their lesions  
347 were more active. Anti-VEGF drug type was not considered in the present analysis because  
348 previous studies have found no substantial difference between ranibizumab and aflibercept.<sup>31</sup>  
349 Nor did we report switching rates as aflibercept was not yet available as a treatment option  
350 for most of our follow-up period. We note that while switching treatments may be a possible  
351 strategy when the early response is poor, there is currently little if any evidence that  
352 switching anti-VEGF agents provides any obvious benefit.<sup>32</sup>

353 High non-completion rates are common in observational studies, and this study was no  
354 exception; 37% of eyes did not complete 3 years of follow-up during the study period.  
355 Reasons for non-completion were reported for more than a third of the non-completers, with  
356 most due to reasons that were not linked with efficacy. Around 40% of the eyes with a  
357 recorded reason for non-completion were discontinued because further treatment was futile or  
358 the patient declined further treatment. Patients were more likely to drop out if they  
359 experienced early VA loss or their VA was less than 70 letters at the 4th injection. The  
360 change in visual acuity at time of dropout between early response groups followed broadly  
361 similar patterns to those observed in the completers, although the final vision at time of  
362 dropout for the early response groups was, on average, 1-2 lines lower than their respective  
363 completers.

364 In conclusion, the early response, particularly attainment of good vision and change in visual  
365 acuity by the 4th injection, was more strongly associated with 3 year visual outcomes than  
366 visual acuity at the time of starting treatment. As treatment protocols for nAMD generally  
367 begin with 3 monthly injections, the response during this standardised period of treatment  
368 may be useful to guide further treatment.<sup>33</sup>

369

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392 **Figure Captions**

393 **Figure 1.** Predicted visual acuity (VA) over time from longitudinal generalised additive  
394 models partitioned by A) whether VA was  $\geq 70$  letters at the 4th injection, B) absolute change  
395 in VA at the 4th injection, C) length of the induction period and D) maximum rate of VA  
396 change between successive injections. These models included data from completers and non-  
397 completers.

398 **Figure 2.** Percentage of eyes partitioned by (A) VA change at the 4th injection and at 3 years,  
399 and (B) VA change at the 4th injection, VA  $< 70$  or  $\geq 70$  letters at the 4th injection ( $< 70$  and  
400  $\geq 70$  respectively, labelled above bars), and VA  $< 70$  or  $\geq 70$  letters at 3 years. Categories for  
401 VA change included early loss ( $< 0$  letter improvement), small gain (1-5 letter improvement)  
402 and large gain ( $> 5$  letter improvement). The number of eyes in each early VA change group  
403 is shown above the bars.

404 **Figure 3.** Kaplan-Meier survival curves of time to non-completion partitioned by A) whether  
405 VA was  $\geq 70$  letters at the 4th injection, B) absolute change in VA at the 4th injection, C)  
406 length of the induction period and D) maximum rate of VA change between successive  
407 injections

408

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- 505

**Table 1.** Demographic characteristics of eyes grouped by their early response to treatment.

	Good Vision Achieved by 4th Injection		Good Vision Achieved by 4th Injection			Time to Inactive CNV			Maximum Rate of VA Change		
	Overall	VA <70 Letters	VA ≥70 Letters	Early Loss	Small Early Gain	Large Early Gain	Short	Long*	Rapid Loss	Gradual Change	Rapid Gain
Eyes	2051	1169	882	682	422	947	984	1067	368	568	1115
Patients	1828	1088	831	647	412	897	907	1002	352	550	1056
Females, %	61.5%	62.0%	60.8%	59.5%	62.8%	62.3%	62.2%	60.8%	61.4%	61.6%	61.4%
Baseline Age (SD)	79.6 (8.2)	80.7 (7.9)	78.3 (8.3)	79.7 (8.6)	79.4 (7.8)	79.8 (8)	80.7 (7.8)	78.7 (8.4)	79.4 (8.6)	79.2 (8.3)	80.0 (8.0)
Baseline VA (SD)	55.9 (18.7)	46.6 (17.8)	68.1 (11.2)	60.1 (19.1)	63.1 (14.4)	49.6 (18.1)	57.8 (18.4)	54.1 (18.8)	60.3 (16.4)	61.5 (19.2)	51.6 (18.0)
≥70 Letters, n (%)	572 (27.9%)	82 (7.0%)	490 (55.6%)	277 (40.6%)	189 (44.8%)	106 (11.2%)	318 (32.3%)	254 (23.8%)	136 (37.0%)	255 (44.9%)	181 (16.2%)
≤35 Letters, n (%)	308 (15.0%)	289 (24.7%)	19 (2.2%)	84 (12.3%)	23 (5.5%)	201 (21.2%)	124 (12.6%)	184 (17.2%)	36 (9.8%)	66 (11.6%)	206 (18.5%)
Baseline Lesion Size, Median μm (Q1, Q3)	2250 (1439, 3200)	2500 (1500, 3500)	1934 (1124, 2800)	2314 (1458, 3300)	2200 (1300, 3158)	2200 (1500, 3200)	2000 (1298, 3000)	2500 (1500, 3500)	2200 (1400, 3306)	2250 (1394, 3300)	2250 (1500, 3199)
Lesion Type, %											
<i>Occult</i>	56.6%	55.4%	58.2%	55.7%	64.2%	53.9%	57.5%	55.8%	60.1%	55.3%	56.1%
<i>Minimally Classic</i>	14.2%	14.5%	13.9%	14.5%	11.1%	15.4%	12.7%	15.7%	13.0%	13.4%	15.1%
<i>Predominantly Classic</i>	20.5%	21.6%	18.9%	21.1%	16.45%	21.9%	20.7%	20.2%	20.1%	20.1%	20.8%
<i>Other</i>	7.3%	7.4%	7.1%	7.3%	7.3%	7.3%	7.4%	7.2%	6.2%	9.0%	6.85%
<i>Not Recorded</i>	1.4%	1.0%	1.8%	1.3%	0.9%	1.6%	1.6%	1.1%	0.5%	2.3%	1.2%

\* Includes 222 persistently active eyes whose lesion has yet to be graded as inactive by the end of completing 3 years of follow-up (69 eyes) or at their most recent visit if they did not complete 3 years of follow-up (153 eyes)

**Table 2.** Association between definitions of early response and achieving good vision ( $\geq 70$  letters) at 3 years. Odds ratios and their respective p-values are presented only for categorical variables. Significant p-values are highlighted in bold.

<b>Categorical Early Response Definitions</b>	<b>VA &lt;70 Letters at 3 Years, n (%)</b>	<b>VA <math>\geq 70</math> Letters at 3 Years, n (%)</b>	<b>Odds Ratio for Achieving <math>\geq 70</math> Letters at 3 Years (95% CI)</b>	<b>P-value</b>	<b>Marginal R<sup>2</sup></b>	<b>AIC</b>
Overall	681 (53%)	608 (47%)	-			
Good VA at Baseline						
VA <70 Letters	574 (64%)	321 (36%)	1	<0.001	0.17	1606
VA $\geq 70$ Letters	107 (27%)	287 (73%)	4.50 (3.30, 6.14)			
Good VA Achieved by 4th Injection						
VA <70 Letters	511 (77%)	149 (23%)	1	<0.001	0.30	1433
VA $\geq 70$ Letters	170 (27%)	459 (73%)	9.78 (6.50, 14.70)			
Absolute Change in VA from Baseline at 4th Injection						
<i>Early Loss</i>	248 (62%)	152 (38%)	1	<0.001*	0.08	1711
<i>Small Early Gain</i>	135 (48%)	148 (52%)	1.75 (1.17, 2.61)			
<i>Large Early Gain</i>	298 (49%)	308 (51%)	1.76 (1.25, 2.45)			
Time to Inactive CNV						
<i>Short Induction</i>	300 (47%)	341 (53%)	1.59 (1.23, 2.07)	<0.001	0.07	1715
<i>Long Induction</i>	381 (59%)	267 (41%)	1			
Maximum Rate of VA Change						
<i>Rapid Loss</i>	141 (62%)	86 (38%)	1	<b>0.011</b> †	0.07	1720
<i>Gradual Change</i>	165 (49%)	175 (51%)	1.70 (1.09, 2.64)			
<i>Rapid Gain</i>	375 (52%)	347 (48%)	1.55 (1.05, 2.30)			

Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

\* Early Loss vs. Small Early Gain (P = 0.002), Early Loss vs. Large Early Gain (P < 0.001), Small Early Gain vs. Large Early Gain (P = 0.986)

† Rapid Loss vs. Gradual Change ( $P = 0.015$ ), Rapid Loss vs. Rapid Gain ( $P = 0.018$ ), Gradual Change vs. Rapid Loss ( $P = 0.523$ )

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<i>Early Loss</i>	57.2 (22.2)	57.9 (55.5, 60.3)	<0.001*	-5.9 (-7.5, -4.3)	-5.6 (-7.2, -3.9)	<0.001***	0.23	10794
<i>Small Early Gain</i>	65.0 (17.2)	64.4 (61.7, 67.1)		0.7 (-0.9, 2.3)	0.7 (-1.3, 2.6)			
<i>Large Early Gain</i>	64.7 (17.6)	64.7 (62.6, 66.8)		12.8 (11.4, 14.1)	12.8 (11.4, 14.2)			
Time to Inactive CNV								
<i>Short Induction</i>	65.3 (17.9)	64.9 (62.9, 66.9)	<0.001	5.3 (3.9, 6.6)	5.3 (3.7, 6.8)	0.145	0.02	11097
<i>Long Induction</i>	59.6 (20.3)	60.1 (58.1, 62.1)		3.4 (2.0, 4.9)	3.7 (2.2, 5.3)			
Maximum Rate of VA Change per 4 Weeks								
<i>Rapid Loss</i>	57.4 (20.7)	58.0 (55.1, 60.9)	<0.001†	-5.2 (-7.6, -2.8)	-4.7 (-7.0, -2.4)	<0.001††	0.14	10937
<i>Gradual Change</i>	63.4 (19.9)	62.8 (60.2, 65.3)		-0.7 (-2.1, 0.7)	-0.9 (-2.8, 1.0)			
<i>Rapid Gain</i>	63.6 (18.4)	63.7 (61.6, 65.7)		9.7 (8.4, 11.0)	9.7 (8.4, 11.1)			

Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

- \* Early Loss vs. Small Early Gain (P < 0.001), Early Loss vs. Large Early Gain (P < 0.001), Small Early Gain vs. Large Early Gain (P = 0.826)
- \*\* Early Loss vs. Small Early Gain (P < 0.001), Early Loss vs. Large Early Gain (P < 0.001), Small Early Gain vs. Large Early Gain (P < 0.001)
- † Rapid Loss vs. Gradual Change (P = 0.006), Rapid Loss vs. Rapid Gain (P < 0.001), Gradual Change vs. Rapid Loss (P = 0.452)
- †† Rapid Loss vs. Gradual Change (P = 0.007), Rapid Loss vs. Rapid Gain (P < 0.001), Gradual Change vs. Rapid Loss (P < 0.001)

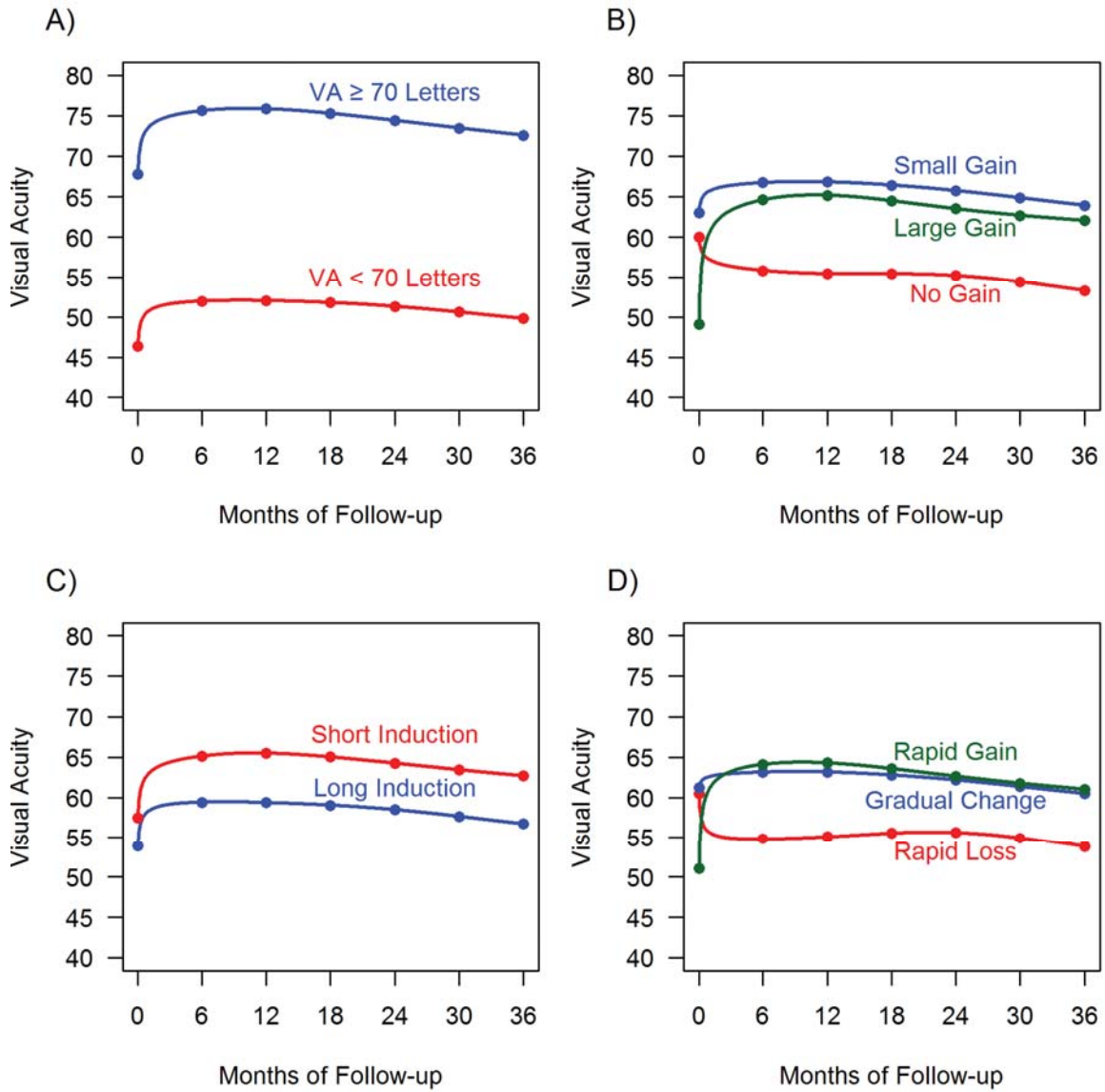
**Table 4.** Visual acuity, change in VA and the proportion of eyes with VA $\geq$ 70 letters at time of dropout, non-completion rates and their association with different definitions of early response. Hazards ratios for non-completion and their respective p-values are presented only for categorical variables. Significant p-values are highlighted in bold.

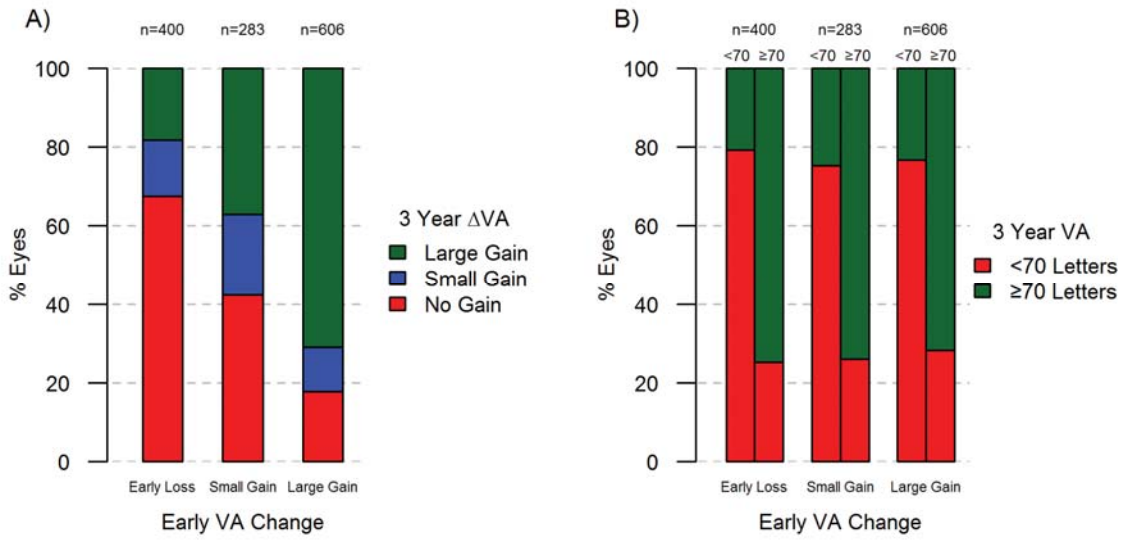
<b>Categorical Early Response Definition</b>	<b>VA at Time of Dropout (SD)</b>	<b><math>\Delta</math>VA at Time of Dropout (95% CI)</b>	<b>VA<math>\geq</math>70 Letters, n (%)</b>	<b>Non-completion Rate, n / N (%)</b>	<b>Hazards Ratio for non-completion (95% CI)</b>	<b>P-value</b>
Overall	52.7 (24.5)	0.6 (-0.9, 2.0)	243 (32%)	762 / 2051 (37%)	-	-
Good VA at Baseline						
VA <70 Letters	46.9 (24.2)	2.0 (0.3, 3.8)	112 (19%)	584 / 1479 (39%)	1	<b>0.003</b>
VA $\geq$ 70 Letters	71.6 (13.8)	-4.3 (6.3, -2.3)	131 (74%)	178 / 572 (31%)	0.77 (0.63, 0.90)	
Good VA by 4th Injection						
VA <70 Letters	43.0 (23.0)	-0.5 (-2.5, 1.4)	52 (10%)	509 / 1169 (44%)	1	<b>&lt;0.001</b>
VA $\geq$ 70 Letters	72.1 (13.4)	2.8 (0.9, 4.7)	191 (75%)	253 / 882 (29%)	0.61 (0.51, 0.71)	
Absolute Change in VA from Baseline at 4th Injection						
Early Loss	46.1 (26.2)	-9.7 (-11.8, -7.6)	78 (28%)	282 / 682 (41%)	1	<b>0.016*</b>
Small Early Gain	59.0 (23.4)	-1.8 (-4.4, 0.9)	61 (44%)	139 / 422 (33%)	0.75 (0.56, 0.93)	
Large Early Gain	55.6 (22.3)	10.0 (8.0, 12.1)	104 (30%)	341 / 947 (36%)	0.85 (0.69, 1.01)	
Time to Inactive CNV						
Short Induction	56.0 (24.0)	2.3 (0.3, 4.3)	129 (38%)	343 / 984 (35%)	0.90 (0.74, 1.05)	0.196
Long Induction	50.0 (24.7)	-0.9 (-2.9, 1.2)	114 (27%)	419 / 1067 (39%)	1	
Maximum Rate of VA Change						
Rapid Loss	44.2 (25.4)	-12.4 (-15.8, -9.0)	32 (23%)	141 / 368 (38%)	1	0.157
Gradual Change	55.2 (25.3)	-2.3 (-4.3, -0.3)	93 (41%)	228 / 568 (40%)	1.05 (0.78, 1.32)	
Rapid Gain	54.3 (23.1)	6.9 (4.9, 8.9)	118 (30%)	393 / 1115 (35%)	0.90 (0.69, 1.11)	

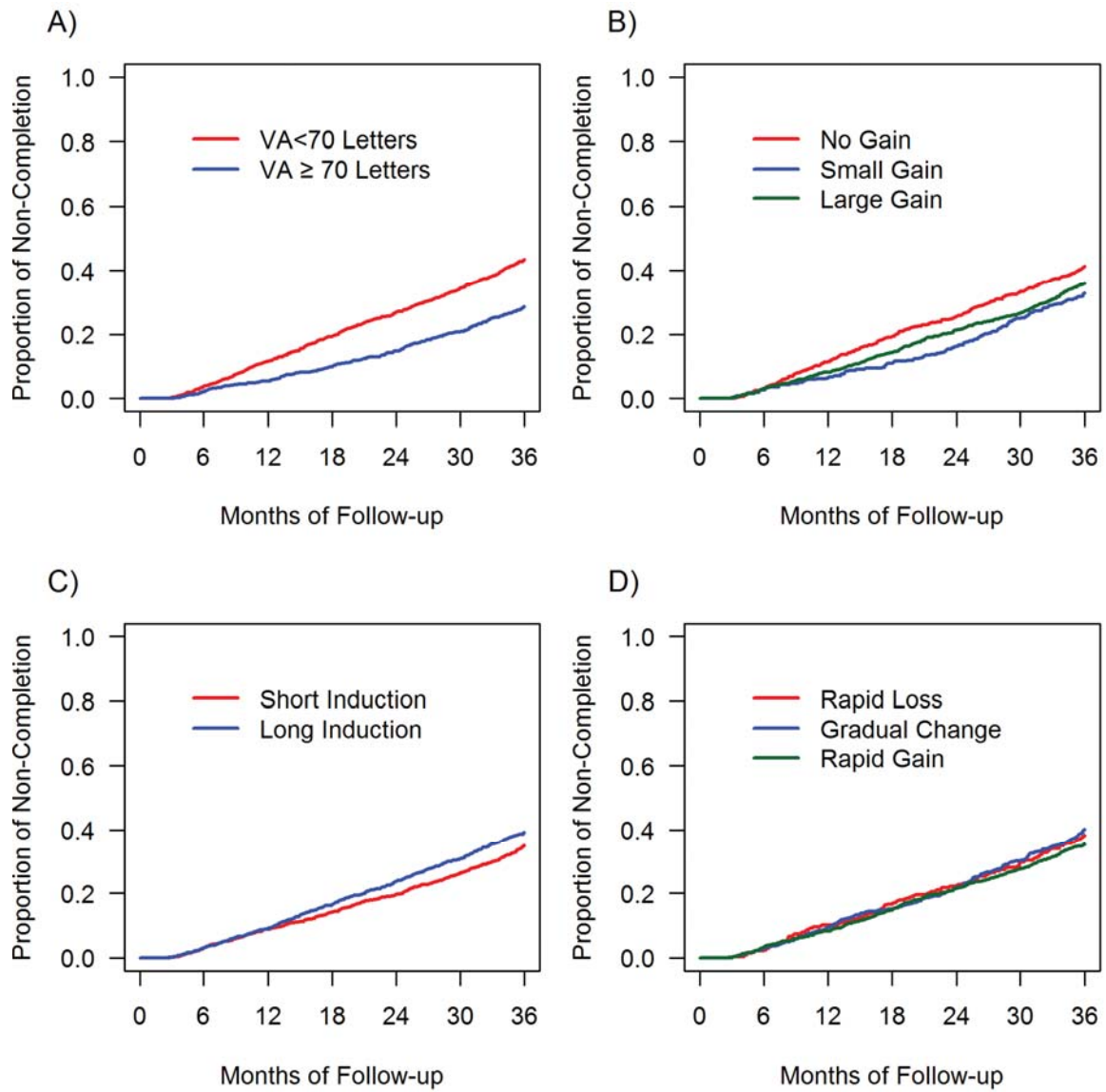
Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

\* Early Loss vs. Small Early Gain ( $P = 0.018$ ), Early Loss vs. Large Early Gain ( $P = 0.100$ ), Small Early Gain vs. Large Early Gain ( $P = 0.206$ )

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The early response to treatment for neovascular age-related macular degeneration is highly associated with treatment outcomes at 3 years and may provide a useful marker for guiding long-term treatment decisions.

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