Progression of Diabetes Retinal Status Within Community Screening Programs and Potential Implications for Screening Intervals

Objective

This study aimed to follow the natural progression of retinal changes in patients with diabetes. Such information should inform decisions with regard to the screening intervals for such patients.

Research design and methods

An observational study was undertaken linking the data from seven diabetes retinal screening programs across the U.K. for retinal grading results between 2005 and 2012. Patients with absent or background retinopathy were followed up for progression to the end points referable retinopathy and treatable retinopathy (proliferative retinopathy).

Results

In total, 354,549 patients were observed for up to 4 years during which 16,196 patients progressed to referable retinopathy. Of patients with no retinopathy in either eye for two successive screening episodes at least 12 months apart, the conditions of between 0.3% (95% CI 0.3–0.8%) and 1.3% (1.0–1.6%) of patients progressed to referable retinopathy, and rates of treatable eye disease were <0.3% at 2 years. The corresponding progression rates for patients with bilateral background retinopathy in successive screening episodes were 13–29% and up to 4%, respectively, in the different programs.

Conclusions

It may be possible to stratify patients for risk, according to baseline retinal criteria, into groups with low and high risk of their conditions progressing to proliferative retinopathy. Screening intervals for such diverse groups of patients could safely be modified according to their risk.

About 5% of the U.K. population has received a diagnosis of diabetes, and the prevalence of both type 1 diabetes and type 2 diabetes is increasing. The current recommendation in the U.K. is that patients with diabetes who are $12 years of age should have a retinal examination at least annually. Those patients found to have potentially sight-threatening diabetic retinopathy (defined as moderate nonproliferative disease or worse and/or diabetic macular edema) are referred to specialist ophthalmology clinics for further assessment and for treatment if required.

Treatment with laser for proliferative disease and for clinically significant macular edema has been shown to reduce the risk of vision loss (1,2). More recently, intravitreal vascular endothelial growth factor therapy has been shown to improve vision in patients with diabetic macular edema (3–5).

The rate of progression from no base-line retinopathy to referable diabetic eye disease has been shown to be <2% at 2 years (6,7), and lower for patients with newly diagnosed disease (8) and other defined groups (9). Retinal screening programs in Wales (n = 49,763) reported that in patients with type 2 diabetes and no baseline retinopathy, 1.2% were referred to an eye clinic over 4 years of follow-up (10). In an English regional program (n = 16,444), the rate was 1.3% over 5 years (11). In Scotland (n = 155,114), the rate was <0.3% for patients who had 2 years of follow-up and had two successive screening episodes without retinopathy (12). A recent systematic review (13) has also suggested that screening every 2 years may be safe for patients with no base-line retinopathy. Comparisons among studies are difficult as study populations, screening criteria, imaging, and grading protocols vary. However, in summary, these studies appear to show that for patients with diabetes and without baseline retinopathy, the proportion who progress toward referable diabetic eye disease is ~0.5–0.6% at 2 years and ~1.2% at 4 years.

Recent work showed that the conditions of patients with no diabetic retinopathy in either eye in each of two consecutive baseline sets of images progressed to sight-threatening diabetic retinopathy at an annual

rate of 0.7%, while that of patients with background retinopathy (BR) in one eye progressed at only 1.9% per year and that of those with background diabetic retinopathy in both eyes at baseline progressed at an annual rate of 11% (14). This risk stratification is useful in the U.K. screening programs because, unlike other risk estimation models proposed (15), it requires no clinical or demographic information.

Within a multicenter retrospective cohort study, we aimed to estimate the rates of progression of diabetic retinopathy in people with diabetes under- going routine regular retinal screening and to explore the potential implications for optimal screening intervals for different risk groups.

Research design and methods

Seven diabetic retinal screening programs voluntarily contributed data to this study, including whole nation programs in Wales, Scotland, and Northern Ireland, and the following four English regional programs: Brighton, Derbyshire, Leeds, and Staffordshire. English programs were chosen from a reduced list of the 84 English programs with a minimum of 10,000 screened patients in 2005, and a grading system that was not known to have given rise to any quality assurance concerns in the previous 5 years. Centers had a variety of geographical locations and differed according to their sociodemographic characteristics.

A data set was defined comprising core demographic information for each anonymized patient linked with screening episode results. Data were sent by participating programs to Public Health England (originally Yorkshire and Humber Public Health Office), who cleaned and prepared the data for analysis. Arrangements were made for secure and confidential data transfer. Before commencing the study, we consulted with the chair of a research ethics committee who gave the opinion that because the data were fully anonymized there was no need for ethical review by a research ethics committee in England. Caldicott Guardian approval was given for use of the Scottish data.

Criteria for data to be used in the analysis included having screening and grading results between 1 January 2005 and 2012 (extraction dates between March and November); at least three grading episodes with fully graded images of both eyes; and the first two episodes with no referable diabetic retinopathy (NR).

The grading protocols differed across the screening centers. The criteria for grading no retinopathy were no diabetes-related abnormality seen on the photograph. Referable retinopathy was defined as moderate nonproliferative diabetic retinopathy (NPDR) (equivalent to a National Health Service [NHS] Diabetic Eye Screening Programme [DESP] score R2 [preproliferative retinopathy]), venous beading, venous reduplication, intraretinal microvascular abnormality, multiple deep round or blot hemorrhages (Early Treatment of Diabetic Retinopathy Study [ETDRS] scale score 43–53), or proliferative retinopathy (ETDRS minimum scale score 61) in all centers. Referable maculopathy was defined as exudate within 1 disc diameter of the center of the fovea, circinate, or group of exudates within the macula or any microaneurysm or hemorrhage within 1 disc diameter of the center of the fovea, but only if associated with a best visual acuity of <0.3 logMAR (equivalent to Snellen test result of 6/12) for the centers in England. In the Scottish centers, referral maculopathy was defined as any blot hemorrhage or hard exudate within 1 disc diameter of the fovea.

Referable diabetic eye disease was a composite term for referable retinopathy and referable maculopathy combined. Eyes disease requiring immediate treatment was termed “treatable diabetic eye disease” and comprised patients with proliferative retinopathy (ETDRS scale score $61).

Patients were categorized according to baseline retinal findings of NR and then into nine ranked risk subgroups according to either the absence of any retinopathy in both eyes (i.e., NR) or the presence of BR (microaneurysms, retinal hemorrhages, any exudate, and ETDRS scale score 20–35) in one or both eyes in the first and second (“base-line”) screening episodes (14) (first episode/second episode). Risk levels were defined as follows: level 1 as BR in both eyes/BR; level 2 as BR in one eye/BR in both eyes; level 3 as NR in both eyes/BR in both eyes; level 4 as BR in both eyes/ BR in one eye; level 5 as BR in one eye/ BR in one eye; level 6 as NR/BR in one eye; level 7 as BR in both eyes/NR; level 8 as BR in one eye/NR; and level 9 as NR/NR on both screening episodes.

Analyses were based on electronic data from each of the seven centers. Screening data for each patient was recoded to assign a risk category using the results of the first two screening episodes after 1 January 2005. For each patient, data from subsequent screening episodes was coded as an event or not, with an event

being the first screening episode with referable diabetic eye disease. Data were plotted using Kaplan- Meier estimates to show the cumulative percentage of patients in whom referable diabetic eye disease developed. In order to estimate the proportions of people with referable diabetic eye disease, we performed survival analysis, defining the time to event as the time from the baseline screening to the development of referable diabetic eye disease at a subsequent screening episode; hence, this was interval censored. Specifically, for those people in whom referable diabetic eye disease did not develop, the time to event was right censored at the date of the last screening, and for those people in whom referable diabetic eye disease developed, the data were left censored at the date of the last screening at which no referable diabetic eye disease was found and with event time at the date of the image set when referable diabetic eye disease was found. Estimates of the proportion of patients in whom referable diabetic eye had developed were obtained using log logistic parametric survival regression models with SAS Proc Lifereg.

Results

In total 354,549 patients were included from the seven centers across the U.K. There were 1,023,207 person-years of observation (median 3 years, interquartile range 24–47 months). Patients were categorized into nine ranked risk sub-groups according to either the absence of any retinopathy or the presence of BR, (microaneurysms, retinal hemorrhages, any exudate, and ETDRS scale score 20–35) in one or both eyes over the two baseline screening episodes. The median number of screening episodes per person included was five (i.e., two baseline episodes and three follow-up episodes).

The size of the seven programs varied from 19,358 to 138,077 patients with diabetes. The median ages varied from 60.8 to 63.9 years (37.8–48.0% were <60 years of age), with 41.9–44.5% being female and 5.9–10.4% having type 1 diabetes. The median duration of diabetes varied from 2 to 4 years.

Overall, there were 16,196 cases of referable retinopathy during the study follow-up period. The rate of progression of retinopathy was related to the baseline retinal findings (Fig. 1). Analysis was undertaken for three of nine possible risk groups. The risk groups were as follows: high risk (NHS DESP score R1/R1 [risk level 1]), medium risk (NHS DESP score R1/R0 [risk level 5]), and low risk (NHS DESP score R0/R0 [risk level 9]). The intermediary risk groups showed a step-wise change in risk, as expected, although in many regions, patients in risk category 6 showed a lower risk than expected, sometimes less than those in risk category 7. The rates of progression from no retinopathy to referable diabetic eye disease in high-risk, medium-risk, and low-risk groups at 1, 2, 3, and 4 years are shown in Tables 1, 2, and 3. There was a low rate of referable eye disease after 2 years in the low-risk group at 0.3–1.3%, and this steadily increased in the intermediate-risk group (2–9%) and higher-risk groups (13–29%). The rate of treatable disease was notably lower in all groups: <0.3% in the two lower-risk groups and 0.5–4.1% in the high-risk group.

The Kaplan-Meier survival curves of progression to referable retinopathy for patients with high to moderate–risk and low-risk baseline retinopathy, are shown in Fig. 1. They show variation among the different programs.

Conclusions

The risk of future referral to ophthalmology for patients with no diabetic retinopathy at baseline after two screening episodes with no diabetic retinopathy was low, ranging from 0.4% to 1.3% at 2 years. In contrast, the risk of referable diabetic eye disease for patients with BR in both eyes at baseline was very high, ranging from 8% to 15% at 1 year. However, usually only patients with proliferative retinopathy require immediate treatment at the first visit to an ophthalmology clinic. In patients with no base-line retinopathy, all centers, except one, reported the development of proliferative retinopathy in <0.1% of patients at 2 years. The final center reported a rate at 0.27%. The comparable estimates at 3 years were 0.1–0.5%. For our high-risk group (those with mild NPDR in both eyes at two successive screening episodes), rates of the development of proliferative retinopathy were between 0.6% and 4.0% after 2 years, and be- tween 0.9% and 6.4% after 4 years. After 2 years of follow-up, patients who had no retinopathy in either eye for two successive screening episodes appear to have a very low risk of the development of diabetic eye disease requiring immediate treatment, and rates requiring referral to an eye clinic that are well below the current annual referral rate of

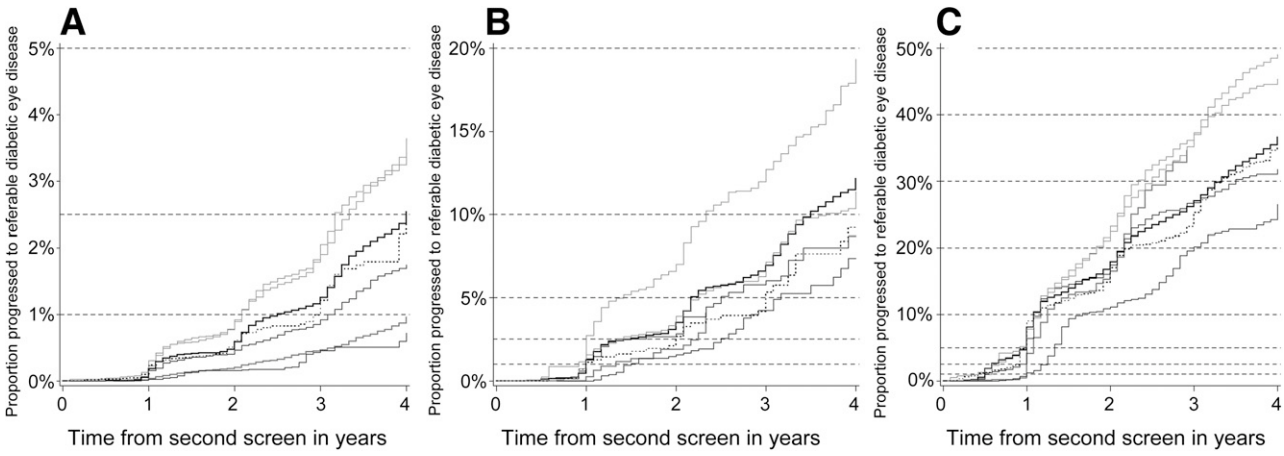

Figure 1—Progression to referable eye disease from mild NPDR or no retinopathy for the seven retinal screening programs. *A*: No diabetic retinopathy in each of two successive screenings. *B*: Mild NPDR in one eye at each of two successive screenings. *C*: Mild NPDR in both eyes on two successive screenings.

~3% (16,17).

This low-risk group of patients accounts for between one-half and two-thirds of patients within these U.K. retinal screening populations. These low referral rates are in keeping with those in previous observational studies (6–12), and they help to define the even lower rates of newly identified treatable disease. It would be possible to further refine the risk categories using additional predictive criteria (e.g., duration of diabetes, HbA_{1c} level, blood pressure, and others). However, not all U.K. retinal screening programs currently have information on other clinical risk factors for retinopathy, so these cannot practically be used for risk stratification and could not be used for this study.

The heterogeneity in results among these seven U.K. centers is an important finding, and may reflect screened populations with different age, sex, and ethnicity profiles, and glycemic and blood pressure control. It may also reflect differences in screening protocols, screening uptake, the completeness of the screening register, and the use of exclusion criteria. However, the variability may also reflect differences in grading. Different quality assurance procedures were used across the centers. The standardization of grading protocols and quality assurance may reduce the variation currently observed among centers. Masked standard image sets and automated grading could be used to enhance within program quality assurance processes.

Screening for diabetic retinopathy was introduced at annual intervals for pragmatic and administrative reasons. However, there was no evidence base that this is the best screening interval. Modern computerized systems make variable screening intervals feasible. Since the pivotal Wisconsin Epidemiologic Study of Diabetic Retinopathy studies (18,19), the nature of diabetes care has changed, with earlier diagnosis; more young patients with type 2 diabetes; and lower targets for HbA_{1c} levels, blood pressure, and cholesterol, all resulting in a lower prevalence of treatable diabetic eye disease (20,21) than in earlier years. In Iceland and parts of Sweden, low-risk individuals are currently screened every 2 to 3 years (9,22). These programs, however, are relatively small, and it is difficult to know how generalizable they are. For instance, in the Swedish study (9) only patients with type 2 diabetes were included and the mean Hba_{1c} level was 6.4%, which is lower than in many regions. However, the accumulating evidence base indicates that screening at 2-year or 3-year intervals for patients with no retinopathy on two consecutive occasions (i.e., a low-risk group) should be safe within a high-quality screening program.

The proportion of patients progressing toward referable diabetic eye disease in our higher-risk categories ranged from 8% to 15% 1 year after baseline measurements and was much greater than in the lower-risk groups. It may be appropriate for these high-risk patients to be screened every 6 months. The

proportion of patients in this high-risk group ranges from 2% to 7% and is much smaller than in the low-risk group. Implementing a variable screening interval for low-risk and high-risk patients is dependent on programs ensuring consistent, highly sensitive screening, with robust software allowing for accurate call/recall of patients. To maintain such standards, all programs would have to be part of a robust internal and external quality assurance scheme and education for the health-care staff involved.

The main strengths of this study are its scale and the application of a robust method to explore the progression of diabetic retinopathy. The results have implications for risk-based screening intervals. A new data set was collated, leading to analyses that included >350,000 patients and >2 million screening intervals for a risk-stratified population (14).

A criticism of this study is that it is based on retrospective, observational analysis and cannot directly show what the effects of changing screening intervals would be. The ideal study would be a randomized, controlled trial comparing annual screening with risk-based screening intervals of 6-24 months. If the difference in progression to proliferative or severe nonproliferactive disease between 1-year and 2-year intervals is ~0.5 per 1,000 patients, then to achieve 80% confidence of a noninferiority outcome with a censoring rate of 5% over 2 years, >120,000 patients would be required, making such a trial unlikely to be practical. Smaller-scale randomized studies looking at the impact on attendance, however, would be valuable.

One concern about extending screening intervals is loss to follow-up, as it is known that missing one episode of retinal screening has been associated with an increased risk of subsequently requiring laser photocoagulation (23), which is estimated to be threefold higher (24). However, if patients are required to have documented absence of retinopathy at two consecutive baseline screenings over a given minimal interval (e.g., 12–24 months), then patients who are poorly compliant will be unlikely to achieve the criteria for categorization as low risk. Any change would need to be closely monitored for loss to follow-up, although other screening programs in the U.K. such as breast, cervical, and bowel cancer screening operate effectively at 2-year or 3-year intervals.

The study included data from different grading centers. Although this might be seen as a weakness, in that we cannot guarantee uniformity in approach, it can also be seen as a strength; despite this potential variability, there were still consistent observations. This will make the findings more replicable in a "real-world" setting. Our study demonstrates different risk categories based on base-line retinal appearances, but in the future it is possible that HbA_{1c} level, type of diabetes, and time since diagnosis may further refine the risk categories.

By reducing the screening interval to 2 years for low-risk groups, and increasing it to every 6 months for high-risk groups, there would be a reduction of 14–40% in screening episodes across the seven screening programs. This would be based on an expected referable rate of ~2.5%. Extending the screening interval for some clearly identified low-risk patient groups may reduce the burden on patients and allow the redeployment of scarce health-care resources, such as investment in 6-month screening intervals for high-risk patients and systems that encourage the attendance of patients who do not currently accept the offer of screening

Further economic modeling is required to understand the overall impact on health-care system costs. The economic gains of longer screening intervals may be particularly important for poorer nations with burgeoning numbers of patients with newly diagnosed diabetes.

The data from this study identify patients within diabetes retinal screening programs who are at low, medium, and high risk of progressing toward referable diabetic eye disease, and who need review within the ophthalmology department. This study supplies further evidence that it may be feasible and safe to move toward screening low-risk patients at intervals of 2 years, high-risk patients every 6 months, and intermediate-risk patients annually.

Table 1—Expected cumulative proportion with referable diabetic eye disease from baseline BR in both eyes (level 1 high risk) at 1–4 years of follow-up (log logistic model)

	Program						
	1	2	3	4	5	6	7
Baseline DESP score R1/R1 in both eyes for 2 years (*n* at risk)	9,356	1,189	2,393	1,029	1,380	2,871	2,026
Mean length of follow-up after second baseline examination (years)	2.8	1.6	2.2	2.3	2.5	2.6	2.5
whom referable retinopathy developed at							
1 year	13.2% (11.9 to 14.7%)	10.9% (8.2 to 14.5%)	8.3% (5 to 12.5%)	13.7% (9.1 to 18.5%)	13.1% (9.9 to 17.1%)	15.4% (12.6 to 18.6%)	11.3% (8.9 to 14.2%)
2 year	21.4% (19.6 to 23.3%)	18% (11.8 to 26.5%)	13% (8.6 to 19.2%)	28.8% (21.8 to 34.8%)	22.4% (17.6 to 28.1%)	27.5% (23.2 to 32.3%)	19.5% (16.1 to 23.4%)
3 year	28.7% (26.4 to 31%)	20.3% (15.3 to 34.9%)	16.1% (11.9 to 22.4%)	38.3% (31.6 to 45.5%)	26.7% (19.6 to 32.1%)	40.9% (36.9 to 45.1%)	26.3% (22.1 to 31.1%)
4 year	35.4% (32.6 to 38.3%)		20.6% (15.1 to 27.4%)	41.5% (34.4 to 50.2%)	31.3% (22.4 to 38.8%)	46.3% (41.0 to 52.8%)	32.0% (24.7 to 40.6%)
Proportion in whom proliferative retinopathy developed at							
1 year	0.76% (0.45 to 1.28%)	0.28% (0.01 to 5.22%)	0.24% (0.02 to 2.06%)	0.76% (0.05 to 4.65%)	0.66% (0.16 to 2.65%)	0.91% (0.19 to 3.24%)	2.42% (1.26 to 4.59%)
2 year	1.25% (0.71 to 2.06%)	1.52% (0.13 to 8.32%)	0.56% (0.05 to 3.49%)	2.16% (0.33 to 7.53%)	2.3% (0.93 to 5.59%)	2.11% (1.11 to 4.2%)	3.98% (2.35 to 6.67%)
3 year	1.77% (1.17 to 2.67%)		0.78% (0.17 to 3.85%)	2.99% (0.77 to 12.63%)		3.18% (1.84 to 6.02%)	5.45% (3.42 to 8.58%)
4 year	2.65% (1.58 to 4.18%)		0.86% (0.19 to 3.85%)			4.68% (2.36 to 9.05%)	6.38% (4.18 to 11.76%)

Table 2—Expected proportion with referable diabetic eye disease from BR in one eye only (level 5 medium risk) at 1–4 years of follow-up (log logistic model)

	Program						
	1 (*n* = 6,949)	2 (*n* = 1,343)	3 (*n* = 3,486)	4 (*n* =1,678)	5 (*n* = 851)	6 (*n* = 1,643)	7 (*n* = 729)
Mean follow-up period (years)	3.1	1.6	2.4	2.7	2.6	3.0	2.6
Progression to referable retinopathy at							
1 year	2.2% (1.5 to 3.1%)	1% (0.2 to 3.6%)	0.9% (0.1 to 5%)	5% (2.8 to 8.3%)	2.1% (0.7 to 6%)	2.5% (1.3 to 4.8%)	1.8% (0.4 to 7%)
2 year	4.8% (3.6 to 6.5%)	1.5% (0.4 to 8%)	2.7% (0.6 to 8.7%)	9.1% (5.5 to 14%)	3.6% (0.9 to 9.4%)	5.2% (2.9 to 9.2%)	3.8% (1.5 to 9.6%)
3 year	7.9% (5.9 to 10.6%)		3.7% (1.6 to 14.9%)	13.9% (10.1 to 19%)	5.8% (2.2 to 15.9%)	9.1% (5.7 to 14.3%)	5.4% (2.4 to 11.6%)
4 year	11.9% (8.9 to 15.3%)		5.5% (1.9 to 19%)	17.7% (12.5 to 24.5%)	9.3% (3.2 to 22%)	11.7% (7.5 to 17.6%)	7.6% (2.7 to 48.7%)
Progression to proliferative retinopathy at							
1 year	0.05% (0.01 to 0.45%)	*	*	0.28% (0.06 to 1.34%)	0.24% (0.09 to 0.65%)	0.06% (0 to 1.38%)	‡
2 year	0.18% (0.04 to 0.86%)			0.42% (0.12 to 1.49%)	†	0.32% (0.05 to 2.12%)	
3 year	0.27% (0.07 to 1%)			0.56% (0.15 to 1.67%)		0.47% (0.09 to 2.33%)	
4 year	0.48% (0.13 to 1.75%)					0.6% (0.09 to 5.36%)	

*Only one patient progressed to NHS DESP score R3. †Two patients progressed to NHS DESP score R3. ‡No patients progressed to R3.

Table 3—Expected proportion with referable diabetic eye disease from no baseline retinopathy in either eye (level 9, low risk) at 1–4 years of follow-up (log logistic model)

	Program						
	1 (*n* = 88,188)	2 (*n* = 63,619)	3 (*n* = 18,622)	4 (*n* = 23,146)	5 (*n* = 13,255)	6 (*n* = 23,482)	7 (*n* = 12,163)
Mean follow-up period (years)	2.9	3.2	2.2	2.9	2.9	3.3	2.6
Progression to referable disease at							
1 year	0.4% (0.3 to 0.5%)	0.1% (0.1 to 0.3%)	0.1% (0 to 0.4%)	0.6% (0.4 to 0.8%)	0.3% (0.2 to 0.5%)	0.5% (0.3 to 0.8%)	0.3% (0.2 to 0.5%)
2 year	0.9% (0.7 to 1.1%)	0.4% (0.2 to 0.6%)	0.3% (0 to 0.8%)	1.3% (1 to 1.6%)	0.7% (0.4 to 1.1%)	1.1% (0.8 to 1.5%)	0.7% (0.5 to 1.1%)
3 year	1.5% (1.2 to 1.8%)	0.5% (0.3 to 0.9%)	0.4% (0.2 to 2.9%)	2.2% (1.9 to 2.7%)	1.3% (0.7 to 2%)	2.4% (1.9 to 3.1%)	1.3% (0.9 to 2%)
4 year	2.6% (2.1 to 3.2%)	1.1% (0.7 to 1.6%)	0.6% (0.2 to 2.9%)	3.3% (2.7 to 4%)	1.8% (0.9 to 3%)	3.6% (3 to 4.3%)	1.9% (1 to 3.4%)
Progression to proliferative retinopathy at							
1 year	0.01% (0 to 0.05%)	0.01% (0 to 0.06%)	*	0.02% (0 to 0.31%)	0.02% (0 to 0.13%)	0.04% (0.01 to 0.16%)	0.15% (0.07 to 0.35%)
2 year	0.04% (0.01 to 0.12%)	0.05% (0.01 to 0.2%)		0.08% (0.01 to 0.43%)	†	0.07% (0.02 to 0.27%)	0.27% (0.11 to 0.63%)
3 year	0.08% (0.03 to 0.18%)	0.08% (0.01 to 0.25%)		0.12% (0.03 to 0.55%)		0.12% (0.04 to 0.33%)	0.39% (0.17 to 0.86%)
4 year	0.14% (0.07 to 0.34%)	0.1% (0.03 to 0.29%)		0.13% (0.03 to 1.7%)		0.20% (0.08 to 0.46%)	0.5% (0.22 to 1.15%)

*Only two patients progressed to NHS DESP score R3. †Four patients progressed to NHS DESP score R3.

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