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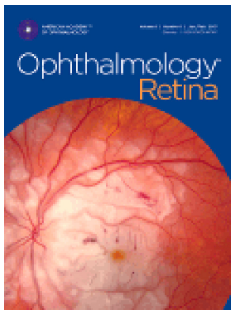

Improved structure and function in early detected second eye neovascular age-related macular degeneration; FASBAT/EDNA report 1

Richard P. Gale, FRCOphth, PhD, Archana Airody, FRCOphth, MD(res), Sobha Sivaprasad, FRCOphth, Rachel L.W. Hanson, PhD, Victoria Allgar, PhD, Martin McKibbin, FRCOphth, Antony B. Morland, PhD, Tunde Peto, Mia Porteous, Usha Chakravarthy, MD, PhD, the FASBAT Study Group

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Improved structure and function in early detected second eye neovascular age-related macular degeneration; FASBAT/EDNA report 1

Running Title:

FASBAT report 1; Improved structure and function in second eyes with nAMD.

Authors:

Richard P. Gale, FRCOphth, PhD [1,2,3] Archana Airody, FRCOphth, MD(res)[2,1], Sobha Sivaprasad FRCOphth[4], Rachel L.W. Hanson, PhD[2,1], Victoria Allgar, PhD[5], Martin McKibbin, FRCOphth[6], Antony B. Morland, PhD[7,3], Tunde Peto[8], Mia Porteous[9], Usha Chakravarthy, MD, PhD[10] and the FASBAT Study Group*

Affiliations:

1. Hull York Medical School, University of York, UK
2. Academic Unit of Ophthalmology, York and Scarborough Teaching Hospitals NHS Foundation Trust, UK
3. York Biomedical Research Institute, University of York, UK
4. NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, UK
5. Peninsula Medical School, University of Plymouth, UK
6. St James's University Hospital, UK
7. Department of Psychology, University of York, UK
8. Centre for Public Health, Queen's University Belfast, Belfast, Ireland
9. Research and Development, York and Scarborough Teaching Hospitals NHS Foundation Trust, UK
10. Centre for Experimental Medicine, Dentistry and Biomedical Sciences, Queen's University of Belfast, UK

Corresponding Author:

Professor Richard P. Gale

The Executive Office, Hull York Medical School, University of York, University Road, Heslington, YO10 5DD

richard.gale@york.ac.uk

*FASBAT Study Group:

Richard P. Gale, York and Scarborough Teaching Hospital (FASBAT Study Chair); Sohba Sivaprasad, Moorfields Eye Hospital; Martin McKibbin, St. James's University Hospital, Leeds; Nicola Hopkins, Colchester Hospital; Louise Downey, Hull Royal Infirmary; Geeta Menon, Frimley Park Hospital; Emily Fletcher, Gloucestershire Royal Hospital; Tunde Peto, Belfast City Hospital; Ben Burton, James Paget University Hospital; Mandeep Bindra, Stoke Mandeville Hospital; Sergio Pagliarini, University Hospitals Coventry & Warwickshire; Faruque Ghanchi, Bradford Royal Infirmary; Sarah MacKenzie, Harrogate District Hospital; Amy Stone, Manchester Royal Eye Hospital; Sheena George, The Hillingdon Hospital; Sanjiv Banerjee, University Hospital of Wales; Konidaris Vasileios, Leicester Royal Infirmary; Steven Dodds, Sunderland Royal Hospital; Savita Madhusudhan, Royal Liverpool University Hospital; Chris Brand, Royal Hallamshire Hospital; Andrew Lotery, Southampton General Hospital; Diane Whistance-Smith, New Cross Hospital; Theo Empeslidis, Leicester Royal Infirmary

Author Contributions:

Conception and Design: Gale, Airody, McKibbin, Sivaprasad, Chakravarthy

Data Collection: Gale, Airody, Sivaprasad, Chakravarthy, McKibbin, the EDNA Study group and the FASBAT Study group

Analysis and Interpretation: Gale, Airody, Hanson, Allgar, Morland, Sivaprasad, Chakravarthy, McKibbin, Tunde Peto and the FASBAT Study group

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Keywords:

Early detection | Neovascular age-related macular degeneration | Fellow eyes | Atrophy | Hyperreflective material | Fibrosis | Intraretinal fluid | Subretinal fluid | Quality-of-life

Abbreviations:

AMD	Age-related Macular Degeneration
VA	Visual Acuity
CFP	Colour fundus photography
CNV	Choroidal neovascularisation
ETDRS	Early Treatment Diabetic Retinopathy Study
IRF	Intraretinal Fluid
nAMD	Neovascular age-related macular degeneration
OCT	Optical Coherence Tomography
SD-OCT	Spectral Domain Optical Coherence Tomography
SHRM	Subretinal hyperreflective material
SRF	Subretinal Fluid

Abstract

Purpose: Visual Acuity (VA) and structural biomarker assessment before and at 24-months after early detection and routine treatment of second eye involvement with neovascular age-related macular degeneration (nAMD) and additional comparison with the first eye affected.

Design: Prospective, 22-centre observational study of participants with unilateral nAMD in the Early Detection of Neovascular AMD (EDNA) study, co-enrolled into the Observing fibrosis, macular atrophy and subretinal highly reflective material, before and after intervention with anti-VEGF treatment (FASBAT) study for an additional 2-year follow-up.

Participants: Older adults (>50 years) with new onset nAMD in the first eye.

Methods: Assessment of both eyes with optical coherence tomography (OCT), colour fundus photography (CFP), clinic-measured visual acuity (VA) and quality-of-life (QoL).

Main Outcome Measures: Prevalence of Atrophy, Subretinal Hyperreflective Material (SHRM), Intraretinal fluid (IRF), Subretinal fluid (SRF) and changes in VA over the study duration in both the first and second eyes affected with nAMD. Composite QoL scores over time.

Results: Of 431 participants recruited to the FASBAT study, the second eye converted to nAMD in 100 participants at a mean of 18.9 months. VA was 18 letters better at the time of early diagnosis in the second eye compared with conventional diagnosis in the first eye (72.9 vs 55.6 letters). 24.9-months post-conversion in the second eye, VA was 69.5 letters compared with at a similar matched time point in the first eye (59.7 letters; 18.9 months). A greater proportion of participants had vision >70 letters in the second eye versus the first eye, 24.9-months post-conversion (61 vs 38). Prevalence of SHRM and IRF was lower in the second eye compared with the first eye at 24.9-months post-conversion to nAMD. However, SRF prevalence was greater in the second eye at 24.9-months post-conversion. The development and progression of total area of atrophy appears similar in both eyes. Mean composite QoL scores increased over time, with a significant correlation between VA for the second eye only 24.9 months post-conversion.

Conclusion: This study has shown that early detection of exudative AMD in the second eye is associated with reduced prevalence of SHRM and IRF and greater visual acuity which is significantly correlated with maintained quality-of-life.

Introduction

Neovascular age-related macular degeneration (nAMD) remains the commonest cause of treatable severe vision loss developed countries, with projections estimating 288 million people affected globally by the year 2040 (1). Usually manifesting unilaterally, onset of nAMD in the fellow, unaffected eye typically occurs in 26-50% of patients within 3 years (2,3). Importantly, fellow eyes treated for nAMD generally show better visual function at diagnosis and over time compared with the first eye, if treatment is commenced promptly (4).

The relationship between morphological characteristics of the retina and change in visual function has identified several retinal biomarkers most pertinent to nAMD disease. It has been long established that atrophy and fibrosis within the fovea are the main drivers of visual loss in AMD (5). A recent systematic literature review has highlighted five key OCT biomarkers related to disease progression in nAMD; subretinal hyperreflective material (SHRM), drusen, intraretinal fluid (IRF), outer retinal tubulations (ORT) and hyperreflective foci, with IRF having the most significant impact on visual outcome (6).

In this study we compare the visual acuity outcomes and prevalence of twelve retinal biomarkers in a cohort of patients with first eye routinely presenting with nAMD and in their second, early detected eyes, up to 24-months post-conversion.

Methods

The observing fibrosis, macular atrophy and subretinal highly reflective material – before and after intervention with anti-VEGF treatment (FASBAT) study was a multicentre, prospective, observational study extending from the Early Detection of Neovascular Age-related macular degeneration (EDNA) study. The EDNA study compared the diagnostic accuracy of optical coherence tomography (OCT), self-monitoring with an Amsler grid, self-reported visual function, slit lamp examination and dye based angiography for early detection of nAMD in the second eye of those already undergoing routine care for nAMD in their first eye (3). The FASBAT study was conducted in twenty-two National Health Service (NHS) ophthalmology departments across the United Kingdom from December 2018 to February 2022. Ethical approval was granted by the NHS Research and Ethics Committee (IRAS: 197731). Written informed consent was obtained from all study participants, and the study followed the tenets

of the Declaration of Helsinki, Good Clinical Practice guidelines and International Council for Harmonization.

Participants

Participants were approached to co-enrol in the FASBAT study at the point of enrolment, at a subsequent date during enrolment or following their involvement in the EDNA study. Participants had to meet the inclusion/exclusion criteria specified to join the EDNA study (3) and be willing to provide data for both eyes for an additional 2 years following their exit from the EDNA study, attending FASBAT study visits with appropriate imaging. In brief, EDNA inclusion/exclusion criteria stipulated that participants were required to have newly diagnosed nAMD in the first eye and an unaffected fellow eye confirmed to be free of nAMD by FFA and with a VA of ≥ 68 ETDRS letters with no confounding retinal pathology.

Study Outcomes

This prospective study was conducted to assess the prevalence of key retinal biomarkers (Table 1) pertinent to nAMD development up to 24-months post-conversion. Similar matched timepoints following conversion to nAMD in both eyes were analysed in order to compare the prevalence of key biomarkers in both the first and second eye. Visual acuity trajectories of both eyes were also studied.

In this study, the 'baseline' timepoint refers to the point of recruitment into the EDNA study, when the first eye had a diagnosis of nAMD. The point in which the second eye converted to nAMD is referred to as to the 'conversion' timepoint. Therefore, baseline for the first eye and conversion for the second eye represent a similar matched timepoint for development of nAMD. The point of conversion of the second eye was at a mean of 18.9 months. This timepoint was used to make similar comparisons of biomarkers in the first eye with the pre-planned 24-month conversion in the second eye.

Quality-of-life was assessed at each timepoint using the National Eye Institute Visual Functional Questionnaire (NEI VFQ) assessment. Composite scores were compared at matched timepoints and a Pearson correlation made between visual acuity in either the first or second eye.

Assessments

Participants were treated following NHS standard care which was defined by the treating physician and could have been a treat-and-extend, as required or fixed regimen. Study-related assessments were carried out at routine NHS standard care clinical visits coinciding with the key study milestone visits (baseline, conversion, post-conversion), for both eyes.

Retinal Imaging. Optical coherence tomography (OCT) and colour fundus photography (CFP) and fluorescence angiography (FA) were captured at each interval using local protocols. All images collected during the FASBAT study were analysed by the reading centre (Central Angiographic Resource Facility) in Belfast following a study-specific protocol. Definitions of the retinal biomarkers are listed in Table 1.

Visual Acuity. Clinic-measured visual acuity (VA) was measured as the number of letters read on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

Quality-of-Life (QoL). National Eye Institute Visual Functional Questionnaire (NEI VFQ) assessed patient reported outcome measures at each time point.

Statistical Analysis

All analyses were completed using SPSS version 26 (IBM, Chicago, IL, USA) following a pre-defined statistical analysis plan.

Results

Participant Characteristics. Of 562 participants recruited to the EDNA study, 431 participants co-enrolled into the FASBAT study for an additional 2-year observational period following completion of the EDNA study (Figure 1). All 431 participants were diagnosed with nAMD in the first eye with dry AMD in the second eye. Of the 431 FASBAT cohort, the second eye remained dry in 314 participants with 117 participants converting to nAMD in their second eye. A total of 56 participants withdrew from FASBAT; of these 17 participants had their second eye convert to nAMD and 38 participants whose second eye remained dry (Figure 1).

This report details characteristics of the 100 participants whose second eye converted to nAMD. Baseline characteristics of the 100 participants are shown in Table 2. The mean

time to conversion in the second eye was 18.9 months (mean: 567.1 days; SD: 309.5 days), ranging from 68-1221 days, with 52% (n=52) converting prior to the mean and 48% (n=48) converting after the mean (Figure 2).

Retinal Biomarker Evaluation

A summary of key retinal biomarkers evaluated in both the first and second eye at similar timepoints from diagnosis of nAMD in each eye can be found in Table 3. The OCT and CFP biomarkers most pertinent to nAMD (6) are discussed. The results of the FA assessment are not reported here.

Subretinal Hyperreflective Material (SHRM). The prevalence of SHRM in the first eye was 93.0% (n=93) at baseline and 92.4% (n=85) at 18.9 months post-conversion. In the second eye, SHRM prevalence was 77.2% (n=71) at conversion and 80.5% (n=70) at 24.9 months post-conversion.

Intraretinal Fluid (IRF). The prevalence of IRF in the first eye 57.7% (n=56) at baseline and 46.5% (n=34) at 18.9 months post-conversion. In the second eye, the prevalence of IRF was 32.9% (n=24) at conversion and 34.1% (n=28) at 24.9 months post-conversion (Table 3).

Subretinal Fluid (SRF). The prevalence of SRF in the first eye was 59.8% (n=58) at baseline 25.4% (n=18) at 18.9 months post-conversion. In the second eye, the prevalence was 35.6% (n=27) at conversion and 28.0% (n=23) at 24.9 months post-conversion (Table 3).

Atrophy (CFP). In the first eye, the prevalence of atrophy was 15.9% (n=14) at baseline and 42.9% (n=33) 18.9 months post-conversion. For the second eye, atrophy prevalence was 17.3% (n=13) at conversion to nAMD and 43.9% (n=25) 24.9 months post-conversion.

Atrophy (OCT). In the first eye, the prevalence of atrophy detected was greater at 31.3% (n=31) at baseline and 55.3% (n=52) 18.9 months post-conversion. For the second eye, atrophy prevalence was 23.4% (n=22) at conversion and 53.5% (n=46) 24.9 months post-conversion.

Visual Acuity

Mean VA in the first eye was 55.6 (SD=15.7) ETDRS letters at the point of diagnosis (baseline), compared with 59.7 (SD=20.5) letters, a mean of 18.9 months post-conversion. In the second eye, the number of ETDRS letters was 72.9 (SD=8.1) at the point of conversion to nAMD and 69.5 (SD=14) letters 24.9 months post-conversion (Table 2). The number of participants gaining and/or losing 15 ETDRS letters in each eye are shown in Figure 3. The proportion of participants with a visual acuity >70 letters in the first eye at 18.9 months post-conversion was 36.5% (n=35) and 65.6% (n=61) in the second eye 24.9 months post-conversion.

QoL

Mean composite score at baseline, when the first eye was diagnosed with nAMD was 73.6 (SD=27.5, n=85). At the point of conversion to nAMD in the second eye, the mean composite score was 70.0 (SD=27.2, n=68) increasing to 76.4 (SD=17.4, n=84) 24.9 months post-conversion in the second eye. A significant Pearson correlated emerged between composite scores and VA for the second eye only 24.9 months post-conversion (R=.429, p=.000, n=80).

Discussion

The FASBAT study reports on the prevalence of a number of key retinal biomarkers, visual acuity and quality-of-life in the first and second eyes of nAMD up to 24-months post-conversion of the second eye. In this observational study of real-world practice, biomarkers were compared at a mean of 18.9 months in the first eye and 24.9 months in the second eye. The FASBAT study was an extension to the EDNA study which evaluated diagnostic accuracy of tools used in the early diagnosis of second eyes.

Across the retinal biomarkers evaluated, it was demonstrated there was a lower prevalence of SHRM and IRF in the second eye compared with the first eye, whilst SRF prevalence was greater in the second eye. Atrophy prevalence was similar between the two eyes. We also reveal greater absolute visual acuity in the second eye of over 10 ETDRS letters at baseline that was maintained across all time points from conversion compared to the first eye. The findings from this study provide strong evidence to monitor the macula of the fellow eye with

OCT regularly to facilitate earlier diagnosis and treatment of nAMD in the second eye to prevent long-term, irreversible damage to retinal structure and function.

In line with previous research, VA in the first affected eye initially increased from 55.6 letters at baseline when the initial diagnosis of nAMD was made, to 59.7 letters at a mean of 18.9 months post-conversion. Both the baseline VA and the +4 letter increase post-conversion is typical of real-world practice in the first eye (7,8). Conversely, at the point of conversion to nAMD in the second eye, VA decreased from 72.9 letters to 69.5 letters at a mean of 24.9 months post-conversion. Whilst this differs to previous research which shows a significantly lower gain in VA in fellow eyes of 0.37±14 letters over 2 years (9), the reduction in VA in our cohort is driven by four individuals who showed reductions in vision >20 letters. Nevertheless, despite the numerical decrease in VA in the second eye, visual performance was consistently better in the second eye compared to the first at approximately 2 years following diagnosis, supporting previous research at 12-months (10,11), 2 years (9), 3 years (4) and real-world datasets (7,8). The proportion of second eyes with good vision (>70 letters) 24-months post-conversion is also in line with previous research at almost double that of the first eye at 65.6% v 36.5%, respectively (9).

This FASBAT study has demonstrated better visual acuity in the second eye. Importantly this study has shown that visual acuity positively correlates with QoL at 24.9 months post-conversion. This underlies the importance of early diagnosis particularly in the second eye, to maintain QoL and prevent significant visual loss for patients with nAMD in the long-term. Economic modelling has also identified that earlier diagnosis of the second eye in nAMD with OCT is indeed cost-effective for patients with nAMD in the first eye (12).

The principal determinants of good visual acuity outcomes in patients with nAMD are the presence and extent of fibrosis, atrophy, IRF and SHRM.

Fibrosis is identifiable as highly reflective material often in the subretinal space (SHRM), although SHRM could also represent fibrin, haemorrhage, neovascular membrane, hyperpigmentation or exudate (6). This study demonstrates there is a lower prevalence of SHRM in the second eye compared with the first eye and this continues to be the case up to 24 months post-diagnosis. We postulate that early diagnosis could therefore lead to less fibrosis, fibrin and identifiable neovascular membrane. It is important to note that Casalino et al. detected a lower prevalence of SHRM in ~66% in their cohort at diagnosis (13), using the same definition (14), perhaps reflecting the inconsistency to grade this biomarker. Since the

commencement of this study there is now consensus nomenclature statement on the definition of SHRM on OCT, defined as 'exudation in the subretinal space of material that is hyperreflective as compared with fluid' (15) which should help with consistency in reporting.

The presence of persistent IRF is associated with worse visual acuity outcomes (6,16). It is pleasing to note that early diagnosis leads to not only less IRF at diagnosis but also out to 24 months post-diagnosis. It is interesting to note that in this real-world setting, the prevalence of SRF at 24 months post-treatment is similar between the first and second eyes. However, persistent SRF, particularly if this is not changing in volume, appears to have less or no detrimental effect on visual acuity in the medium-term (16).

Atrophy was consistently more diagnosed with OCT compared with CFP. We believe this is a combination of the grading definitions used and the ability to detect atrophy on the different imaging modalities. Nonetheless, there appears to be little difference in the prevalence of atrophy diagnosed with either method at diagnosis in the first eye and the second eye and indeed the prevalence increases to a similar extent approximately 2 years post-diagnosis. Therefore, early diagnosis of nAMD does not influence the prevalence of atrophy.

Study Strengths and Limitations

Our study has multiple strengths. FASBAT was a prospective, multicentre study including 22 NHS Trusts across 3 nations of the United Kingdom thus providing real-world evidence from a diverse and representative population of nAMD patients. All imaging data collected were evaluated following reading centre grading which is a further strength of the study.

Our study is not without its limitations. Firstly, due to the observational nature of this study, the matched timepoints for analysis of biomarkers between first and second eyes were not exact; being earlier in the first eye at approximately 18.9 months compared with 24.9 months in the second eye. This could lead to an under-representation of biomarker prevalence that may continue to develop in the first eye. Secondly, at 24.9 months post-conversion for the second eye there was a number of missing data points for between 7 and 41 participants. Unfortunately, for the majority of participants, this time point coincided with the lockdowns and restrictions imposed by the United Kingdom government in response to COVID-19. Thirdly, although FA was used to exclude nAMD in the fellow eye at baseline, multimodal imaging, including structural OCT and OCT-angiography, may reveal the possibility of

neovascularisation at baseline. The likelihood of this is low however, and as such we believe this would not fundamentally change the observed improved structural and functional outcomes with early detection in the second eye. Nevertheless, the FASBAT study still provides important evidence pertaining to retinal changes associated with the development of nAMD in the second eye both before and 2 years post-conversion. Finally, definitions of such biomarkers continue to evolve and there is now consensus nomenclature for many biomarkers, such as atrophy defined by the classification of atrophy meetings program group (17) and hyperreflective material defined by the consensus on neovascular age-related macular degeneration nomenclature study group (15).

In unilateral nAMD, the FASBAT study has shown that in the second eye there is a greater visual acuity and reduced prevalence of pertinent retinal biomarkers post-conversion to nAMD due to early detection of disease onset and after follow-up to 2 years. Currently, OCT is the best imaging modality in terms of diagnostic accuracy (3) of new nAMD and our study results substantiate the need for regular monitoring of fellow eyes of unilateral nAMD to prevent significant changes to retinal structure and function.

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418 **Table 1:** List of the key retinal imaging biomarkers evaluated in the FASBAT study and the
419 reading centre definitions.

Retinal Biomarker	Imaging Modality	Reading Centre Definition
SHRM	OCT	Any hyper-reflective material that obscures normal retinal anatomical features.
IRF	OCT	Hypo-reflective spaces with a minimum vertical diameter of 50 microns.
SRF	OCT	Areas of hypo reflectivity or moderate reflectivity between the neurosensory retina and RPE/BM.
Atrophy	OCT	Increased signal transmission through the RPE/Bruch's complex; RPE band thinning or missing; Outer nuclear layer thinning, missing
	CFP	An area of sharply defined drop out of RPE of at least 175 microns in diameter with two of the following identified; choroidal vessels exposed; well defined margins; scalloped edges.

420 **SHRM: Subretinal Hyperreflective Material; IRF: Intraretinal Fluid; SRF: Subretinal*
421 *Fluid; OCT: Optical Coherence Tomography; CFP: Colour Fundus Photography*

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Table 2: Baseline demographics of the 100 participants whose second eye converted to nAMD

Age (mean, SD)	76,5
Age range (years, months)	59,9 – 92,6
Gender (n, %)	
Male	41 (41)
Female	59 (59)
Mean VA (ETDRS letters)	
First eye at baseline	55.6
Second eye (at point of conversion)	72.9

**SD: Standard Deviation; VA: Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study*

Table 3: Retinal biomarker evaluation of the 100 FASBAT participants whose second eye converted to nAMD.

	First Eye at diagnosis of nAMD (Baseline)	Second Eye at diagnosis of nAMD (Conversion)	First Eye a mean of 18.9 months post-conversion	Second Eye a mean of 24.9 months post-conversion
Atrophy (CFP)				
No (n; %)	74 (84.1)	62 (82.7)	44 (57.1)	32 (56.1)
Yes (n; %)	14 (15.9)	13 (17.3)	33 (42.9)	25 (43.9)
Cannot Grade (n)	0	0	0	2
Missing data (n)	12	25	23	41
Atrophy (OCT)				
No (n; %)	68 (68.7)	72 (76.6)	42 (44.7)	40 (46.5)
Yes (n; %)	31 (31.3)	22 (23.4)	52 (55.3)	46 (53.5)
Cannot Grade (n)	1	0	0	1
Missing data (n)	0	6	6	13
SHRM (OCT)				
No (n; %)	7 (7)	21 (22.8)	7 (7.6)	17 (19.5)
Yes (n; %)	93 (93)	71 (77.2)	85 (92.4)	70 (80.5)
Cannot Grade (n)	0	1	2	0
Missing data (n)	0	7	6	13
SRF (OCT)				
Mean Max Height (µm; SD)	141.6 (125.7)	87 (63.1)	61.8 (83.9)	64.1 (80.6)
n (%)	58 (59.8)	27 (35.6)	18 (25.4)	23 (28)
Mean Foveal Max Height (µm; SD)	98.1 (75.5)	82.5 (73.6)	69.3 (23.1)	73.3 (42)
n (%)	20 (20.6)	10 (13.7)	3 (4.2)	7 (8.5)
IRF (OCT)				
No (n; %)	42 (42.3)	50 (67.1)	38 (38.4)	55 (65.9)
Yes (n; %)	56 (57.7)	24 (32.9)	34 (46.5)	28 (34.1)
Cannot Grade (n)	0	0	0	0
Missing data (n)	2	26	28	17

**CFP: Colour Fundus Photography; OCT: Optical Coherence Tomography; SHRM: Subretinal Hyperreflective Material; SRF: Subretinal Fluid; IRF: Intraretinal Fluid. µm: Microns; SD: Standard Deviation*

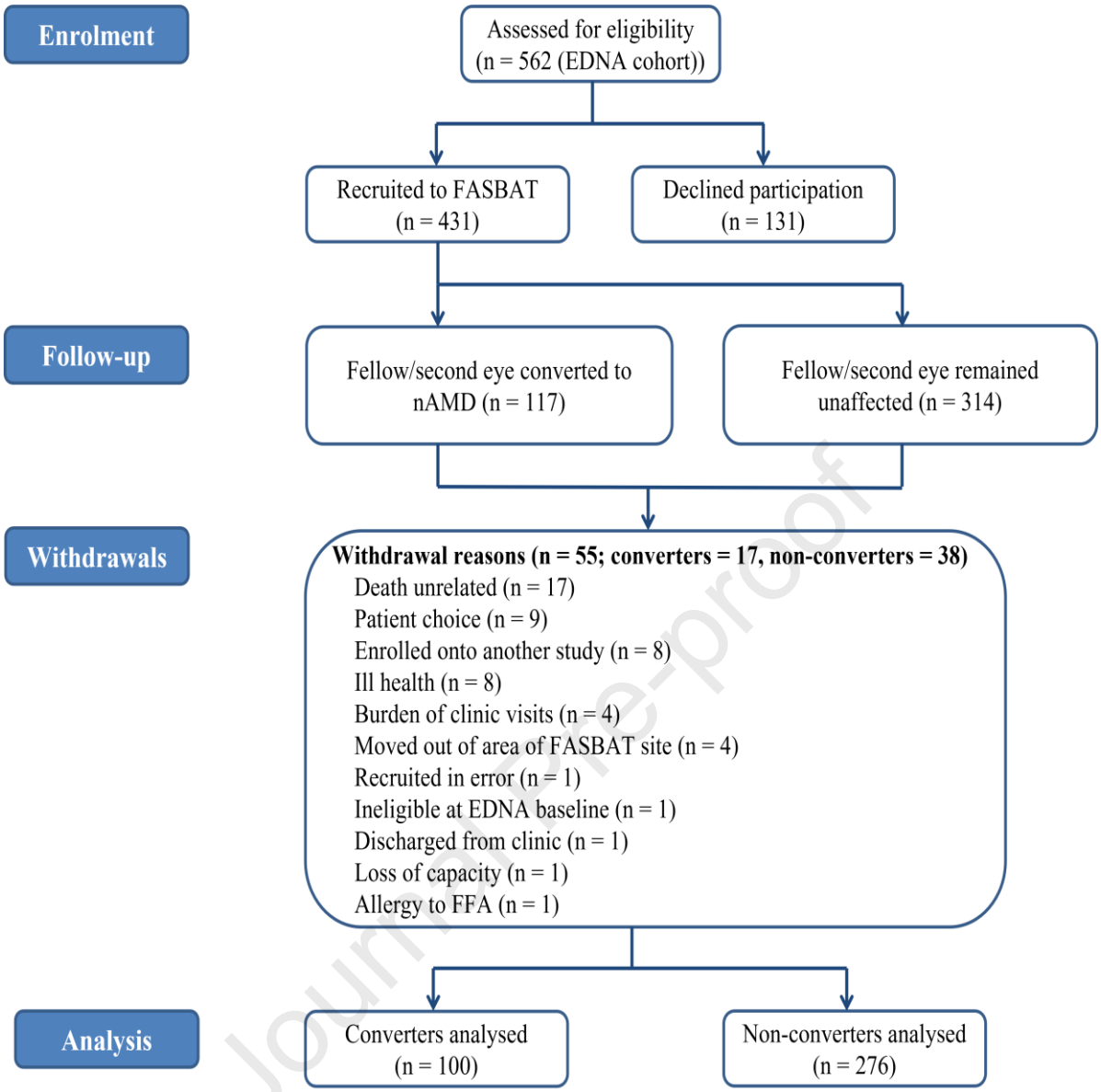

Figure 1: *CONSORT diagram of participant flow through the FASBAT study*

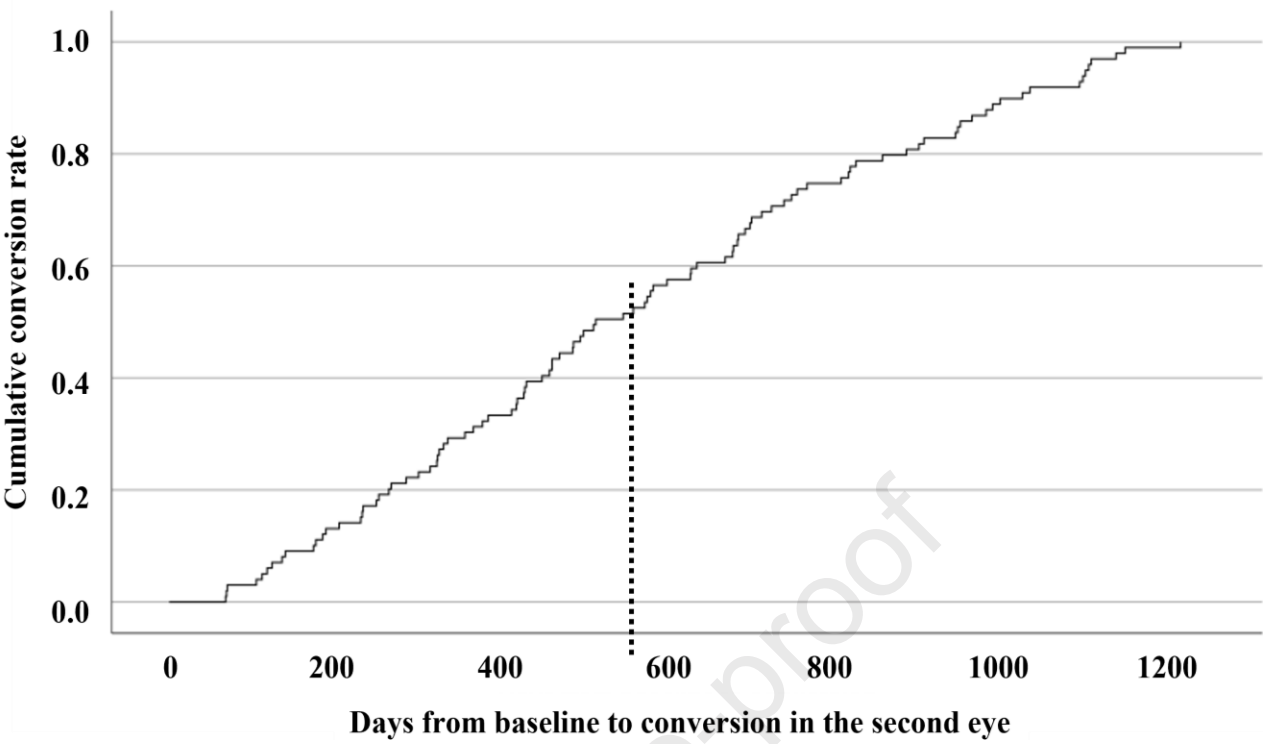

Figure 2: *Distribution of participants whose second eye converted to nAMD. The mean time to conversion, indicated by the vertical dashed line, was 18.9 months (mean number of days = 567.1; SD = 309.5 days), ranging from 2.3 to 40.7 months (68 – 1221 days). There were 52% (n=52) of participants who converted before this mean with 48% (n=48) converting after the mean.*

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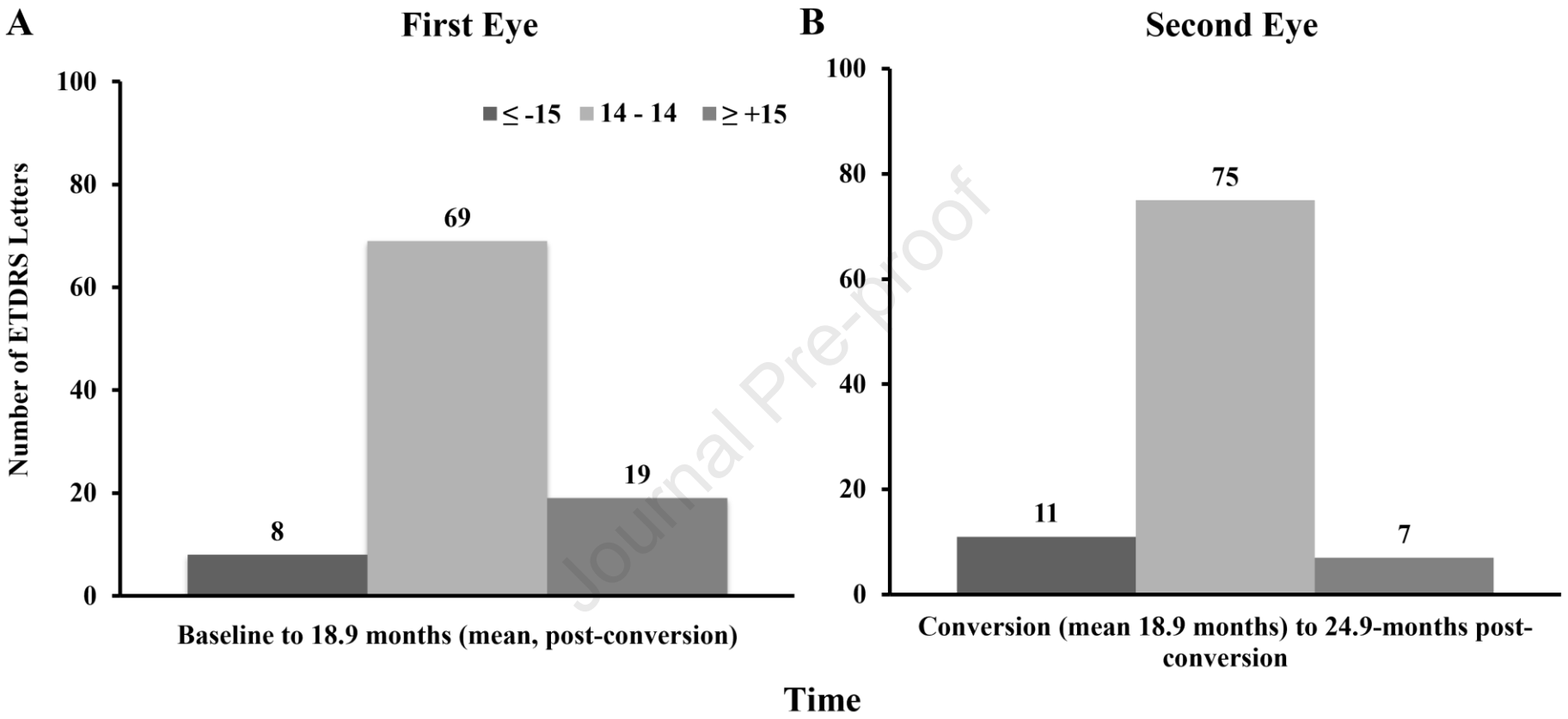

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445 ***Figure 3:*** *The number of participants gaining or losing more than 15 ETDRS letters between baseline and 18.9 months mean, post-conversion in*
446 *the first eye* ***(A)*** *and between the point of conversion and 24.9 months post-conversion in the second eye* ***(B)***.

Table 1: List of the key retinal imaging biomarkers evaluated in the FASBAT study and the reading centre definitions.

Retinal Biomarker	Imaging Modality	Reading Centre Definition
SHRM	OCT	Any hyper-reflective material that obscures normal retinal anatomical features.
IRF	OCT	Hypo-reflective spaces with a minimum vertical diameter of 50 microns.
SRF	OCT	Areas of hypo reflectivity or moderate reflectivity between the neurosensory retina and RPE/BM.
Atrophy	OCT	Increased signal transmission through the RPE/Bruch's complex; RPE band thinning or missing; Outer nuclear layer thinning, missing
	CFP	An area of sharply defined drop out of RPE of at least 175 microns in diameter with two of the following identified; choroidal vessels exposed; well defined margins; scalloped edges.

**SHRM: Subretinal Hyperreflective Material; IRF: Intraretinal Fluid; SRF: Subretinal Fluid; OCT: Optical Coherence Tomography; CFP: Colour Fundus Photography*

Table 2: Baseline demographics of the 100 participants whose second eye converted to nAMD

Age (mean, SD)	76,5
Age range (years, months)	59,9 – 92,6
Gender (n, %)	
Male	41 (41)
Female	59 (59)
Mean VA (ETDRS letters)	
First eye at baseline	55.6
Second eye (at point of conversion)	72.9

**SD: Standard Deviation; VA: Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study*

Table 3: Retinal biomarker evaluation of the 100 FASBAT participants whose second eye converted to nAMD.

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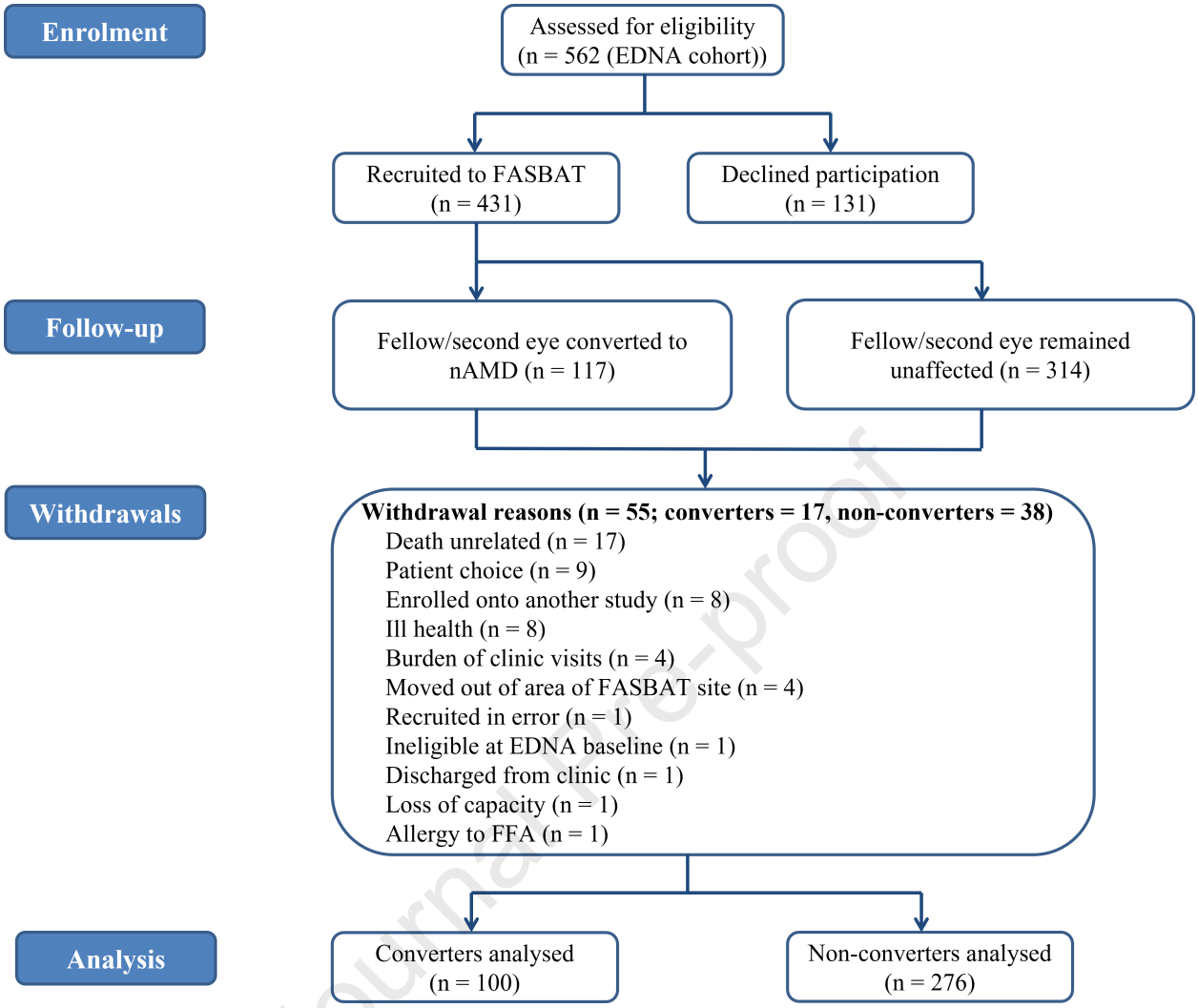

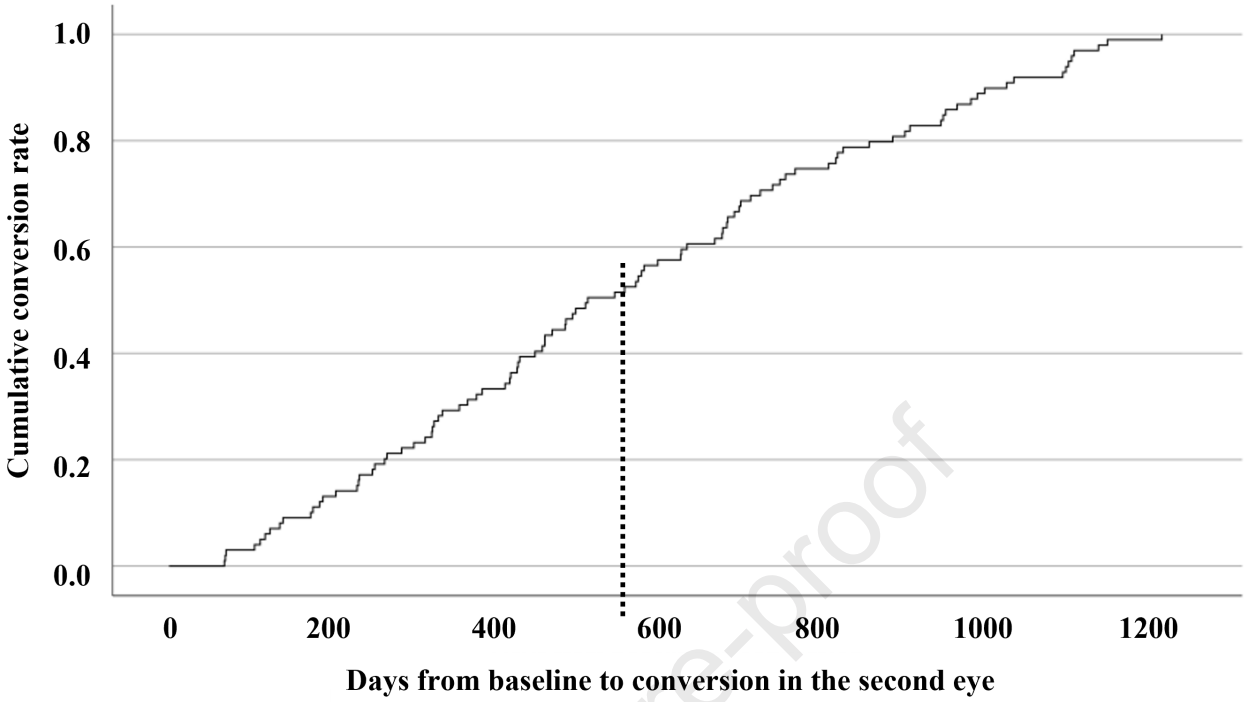

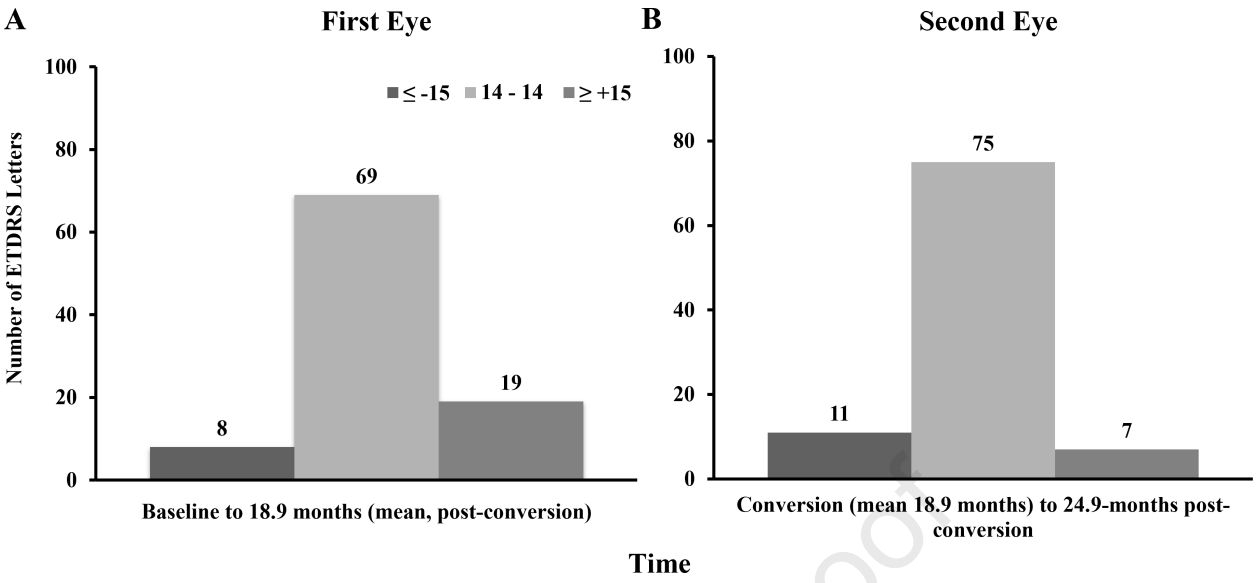

Visual and structural outcomes of eyes with neovascular age-related macular degeneration: FASBAT report 1; An extension to EDNA

Authors:

Richard P. Gale, FRCOphth, PhD [1,2,3] Archana Airody, FRCOphth, MD(res)[2,1], Sobha Sivaprasad FRCOphth[4], Rachel L.W. Hanson, PhD[2,1], Victoria Allgar, PhD[5], Martin McKibbin, FRCOphth[6], Antony B. Morland, PhD[7,3], Tunde Peto[8], Mia Porteous[9], Usha Chakravarthy, MD, PhD[10] and the FASBAT Study Group*

Precise

Early detection of neovascular age-related macular degeneration in the second eye is associated with greater visual acuity and reduced prevalence of pertinent retinal biomarkers up to 24-months post-conversion.

ORET-D-23-00804 – Improved structure and function in early detected second eye neovascular age-related macular degeneration; FASBAT/EDNA report 1

FASBAT Study Group:

Richard P. Gale, York and Scarborough Teaching Hospital (FASBAT Study Chair); Sohba Sivaprasad, Moorfields Eye Hospital; Martin McKibbin, St. James's University Hospital, Leeds; Nicola Hopkins, Colchester Hospital; Louise Downey, Hull Royal Infirmary; Geeta Menon, Frimley Park Hospital; Emily Fletcher, Gloucestershire Royal Hospital; Tunde Peto, Belfast City Hospital; Ben Burton, James Paget University Hospital; Mandeep Bindra, Stoke Mandeville Hospital; Sergio Pagliarini, University Hospitals Coventry & Warwickshire; Faruque Ghanchi, Bradford Royal Infirmary; Sarah MacKenzie, Harrogate District Hospital; Amy Stone, Manchester Royal Eye Hospital; Sheena George, The Hillingdon Hospital; Sanjiv Banerjee, University Hospital of Wales; Konidaris Vasileios, Leicester Royal Infirmary; Steven Dodds, Sunderland Royal Hospital; Savita Madhusudhan, Royal Liverpool University Hospital; Chris Brand, Royal Hallamshire Hospital; Andrew Lotery, Southampton General Hospital; Diane Whistance-Smith, New Cross Hospital; Theo Empeslidis, Leicester Royal Infirmary