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Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors

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ABSTRACT

Clinical trials identified intravitreal vascular endothelial growth factor inhibitors (anti-VEGF agents) have the potential to stabilise or even improve visual acuity outcomes in neovascular age-related macular degeneration (AMD), a sight-threatening disease. Real-world evidence allows us to assess whether results from randomised controlled trials can be applied to the general population. We describe the development of global registries, in particular the Fight Retinal Blindness! registry that originated in Australia, the United Kingdom AMD Electronic Medical Records User Group and the IRIS registry in the USA. Real-world observations relating to efficacy, safety and resource utilisation of intravitreal anti-VEGF therapy for neovascular AMD are then summarised. Novel observations that would have been challenging to identify in a clinical trial setting are then highlighted, including the risk of late disease reactivation, outcomes in second versus first treated eyes, and the increased risk of posterior capsular rupture during cataract surgery in patients who have received intravitreal anti-VEGF therapy. We conclude by exploring future directions in the field. This includes the development of a global consensus on real-world outcome measures to allow greater comparison of results. Real-world neovascular AMD outcome registries can be linked with other databases to determine systemic safety or genetic predictors of treatment efficacy. Machine learning offers opportunities to extract useful insights from “Big Data” often collected in these registries. Real-world registries could be used by drug regulatory authorities and industry as an alternative to more costly and time-consuming phase 4 clinical trials, potentially allowing medication costs to be based on outcomes achieved.

1. Introduction

1.1. Natural history of neovascular age-related macular degeneration and poor prognosis with historic interventions

Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss in developed countries and accounts for 7% of global blindness worldwide (Bourne et al., 2013; Bressler, 2004). The worldwide prevalence of AMD is rising as the population ages, with 288 million people projected to have either the early or late manifestations

of AMD by 2040 (Wong et al., 2014). Late disease is characterised by significant loss of central vision gradually due to geographic atrophy or more rapidly due to development of neovascularisation.

Neovascular (exudative or wet) AMD is characterised by aberrant angiogenesis originating from the choroidal or, less frequently, the retinal circulation (Gass et al., 2003). These aberrant vessels are prone to leakage resulting in fluid accumulation, haemorrhage and fibrosis that can lead to rapid central visual loss compared with atrophic AMD which causes more gradual visual decline. Whilst it occurs in less than 15% of all patients with AMD, neovascular AMD was, at least before the

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advent of vascular endothelial growth factor (VEGF) inhibitors, the cause of over 80% of cases of blind registration (Jager et al., 2008).

The Macular Photocoagulation Study (MPS) (1982) evaluated laser photocoagulation for the management of neovascular AMD. Initially, patients with choroidal neovascular membranes outside the fovea (extrafoveal) were recruited. After 18 months of follow-up, 60% of untreated eyes versus 25% of treated eyes had experienced severe visual loss (defined as loss of six or more letters on a logarithm of the minimum angle of resolution [LogMAR] vision chart) and further recruitment was stopped as there was now clinical trial evidence that a treatment for extrafoveal neovascular AMD could reduce the risk of severe visual loss. However, after 3 years of follow-up, over half (59%) of eyes had recurrent choroidal neovascularisation documented. The MPS Group proceeded to assess laser photocoagulation for neovascular AMD lesions under the fovea (subfoveal) (1991). Even though there were larger losses in vision at 3 months in treated eyes, by 2 years only 21% of treated versus 38% of untreated eyes experienced severe visual loss. The MPS Group also observed that neovascular AMD developed in fellow eyes at a rate of approximately 5% per year during 5 years follow-up (1993).

Several other treatments for neovascular AMD have failed evaluation in randomised controlled trials. The Submacular Surgery Trials research group reported that surgery for subfoveal lesions in neovascular AMD as performed in the clinical trial did not improve or preserve visual acuity compared with observation over 2 years and therefore was not recommended for patients with similar lesions (Hawkins et al., 2004). A single dose of intravitreal triamcinolone had no effect on the risk of loss of visual acuity over 1 year in study eyes with neovascular AMD although there was a reduction in angiographic leakage at 3 months (Gillies et al., 2003). A Cochrane Review (Evans et al., 2010) of trials of external beam and plaque radiotherapy for neovascular AMD did not identify convincing evidence that radiotherapy on its own was an effective treatment.

Clinical trials with verteporfin photodynamic therapy (cold laser plus sensitising dye) were initiated in 1996. The Treatment of AMD with Photodynamic (TAP) Study (Bressler, 2002) reported 59% of eyes with predominantly classic subfoveal lesions in the verteporfin group versus 31% of eyes in the placebo group lost fewer than 15 letters vision from baseline over 2 years. The Verteporfin in Photodynamic Therapy (VIP) Study (Verteporfin In Photodynamic Therapy Study, 2001) reported 45% of eyes with occult lesions with no classic component versus 32% of eyes in the placebo group lost fewer than 15 letters of vision from baseline over 2 years.

The results of the clinical trials discussed above demonstrated that there was a major unmet need for effective treatments for neovascular AMD that could stabilise disease and potentially improve vision rather than just slow disease progression.

1.2. Real-world case reports suggested a role for vascular endothelial growth factor inhibitors (anti-VEGF) in the treatment of neovascular AMD

In 1948, Michaelson described the process of neovascularisation in the retina and hypothesised that a diffusible factor (“Factor X”) was responsible for angiogenesis in hypoxic conditions (Michaelson, 1948). Subsequent studies suggested that this Factor X was vascular endothelial growth factor (VEGF) (Senger et al., 1983; Ferrara and Henzel, 1989; Aiello et al., 1994; Miller et al., 1997; Tolentino et al., 2002).

Animal studies demonstrated inhibition of tumour cell angiogenesis could slow tumour growth (Holmgren et al., 1995; Parangi et al., 1996). One of the first anti-VEGF treatments to be developed was a humanised monoclonal antibody effective against isoform A of VEGF called bevacizumab (Avastin). After successful clinical trials demonstrated increased median survival times with systemic bevacizumab combined with chemotherapy versus chemotherapy alone, systemic bevacizumab was approved for use in the treatment of colon cancer in 2004 (Hurwitz et al., 2004).

Following the approval of a systemic anti-VEGF drug for the treatment of colon cancer and the suspected role of VEGF in neovascular AMD, clinicians used intravenous bevacizumab as an off-label treatment for neovascular AMD. In a prospective case series (Michels et al., 2005) of 18 patients treated with intravenous infusions of bevacizumab, Michels et al. reported a median increase in visual acuity of 8 letters by 12 weeks. Rosenfeld et al. (2005) subsequently published the first report of intravitreal bevacizumab for a case of recurrent neovascular AMD and reported visual benefit. Intravitreal delivery had advantages of lower drug dosage, a better systemic safety profile, easier delivery and lower cost. Retrospective case series provided further evidence that intravitreal bevacizumab might improve visual acuity in neovascular AMD (Spaide et al., 2006; Avery et al., 2006), highlighting the need for robust randomised controlled trials.

1.3. Recording distance visual acuity

Changes in distance visual acuity have been used as the primary endpoint in seminal clinical trials of anti-VEGF therapy for nAMD (see Section 1.4).

The prototype distance visual acuity chart was developed in 1862 by Dutch ophthalmologist Hermann Snellen (Falkenstein et al., 2008). “Standard vision” was defined as the ability to recognise one of his optotypes at a visual angle of 1 min of arc. The original chart was later modified to become what is now known as a Snellen chart. Although widely used, this chart has a number of limitations, such as unequal and unrelated spacing between letters and rows, inconsistent progression in letter size from one line to the next, unequal legibility of letters used, and large gaps between acuity levels at the lower end of the scale.

Bailey and Lovie (1976) introduced new principles for the design and use of letter charts for the measurement of visual acuity. They advocated that the test task should be essentially the same at each size level on the chart. Such standardisation of the test task requires the use of letters of equal legibility, the same number of letters on each row, and uniform between-letter and between-row spacing. They also advocated that, combined with the test task standardisation, there should be a logarithmic progression of letter size. These charts facilitate the use of nonstandard testing distances which might be used when there is low visual acuity or when examination room layout prevents testing at the standard distance. This type of LogMAR chart was further modified by Ferris et al. in 1982 (Ferris et al., 1982) including use of the sans serif font to improve legibility. This LogMAR chart was adopted for the Early Treatment Diabetic Retinopathy Study (ETDRS chart) and later seminal clinical trials. The ETDRS chart is a type of LogMAR chart. Therefore, LogMAR letters can be considered equivalent to ETDRS letters. However, LogMAR letters is a more accurate term.

In a clinical trial setting refracted best-corrected distance VA readings are obtained at important time-points with standard luminance and test distances. In a real-world setting it may not be practical to carry out regular refracted best-corrected distance VA measurements and luminance levels and test distances may vary from visit to visit, potentially leading to less accurate measurements. The International Consortium for Health Outcomes Measurement Macular Degeneration Standard Set recommends recording the best of uncorrected distance VA, corrected distance VA using glasses or contact lenses, or pinhole if required in the affected eye at each clinical visit in the real-world setting (Rodrigues et al., 2016).

All visual acuity outcomes are reported in LogMAR letters in this review. Table 1 provides a conversion table between Snellen distance visual acuity and LogMAR distance visual acuity.

1.4. Seminal phase 3 clinical trials of intravitreal anti-VEGF therapy for neovascular AMD

1.4.1. Pegaptanib

One of the initial intravitreal anti-VEGF treatments developed specifically for neovascular AMD was pegaptanib (Macugen), a single

Table 1
Conversion table between Snellen and LogMAR distance visual acuities.

Snellen (feet)	Snellen (metres)	LogMAR	LogMAR letters (equivalent to number of ETDRS letters read)
No Perception of Light			0
Perceives Light			1
Hand Movements			2
Count Fingers			3
20/800	6/240	1.6	4
20/630	6/190	1.5	5
20/500	6/150	1.4	10
20/400	6/120	1.3	20
20/320	6/95	1.2	25
20/250	6/75	1.1	30
20/200	6/60	1.0	35
20/160	6/48	0.9	40
20/125	6/38	0.8	45
20/100	6/30	0.7	50
20/80	6/24	0.6	55
20/63	6/19	0.5	60
20/50	6/15	0.4	65
20/40	6/12	0.3	70
20/32	6/9.5	0.2	75
20/25	6/7.5	0.1	80
20/20	6/6	0.0	85
20/16	6/4.8	-0.1	90
20/12.5	6/3.8	-0.2	95
20/10	6/3	-0.3	100

stranded nucleic acid aptamer that binds specifically to the 165 isoform of VEGF hence antagonising its action. Subsequent trials demonstrated that not only could pegaptanib reduce the rate of visual loss, it could also lead to maintenance or improvement of vision in patients with neovascular AMD compared to placebo (Gragoudas et al., 2004). Pegaptanib was approved by the United States Food and Drug Administration (FDA) in 2004 for treatment of neovascular AMD (F.D.A., 2005). However, visual gains were not as impressive as later less specific anti-VEGF agents and pegaptanib is no longer commonly used for subretinal neovascularisation.

1.4.2. Ranibizumab

It was postulated that bevacizumab, which is a full length anti-VEGF antibody, would be too large to sufficiently diffuse through the retina to reach the choroid. This led to the development of ranibizumab (Lucentis) for intravitreal administration, which is essentially a Fab fragment of bevacizumab with increased binding affinity and inhibition of the growth factor (Steinbrook, 2006). The Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular Age-related macular degeneration (MARINA) and Anti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularisation in age-related macular degeneration (ANCHOR) were two seminal randomised controlled trials that demonstrated the benefits of ranibizumab for neovascular AMD (Kaiser et al., 2007; Rosenfeld et al., 2006; Brown et al., 2006).

The MARINA trial randomised patients to ranibizumab 0.3mg, 0.5mg and sham injections for a period of 24 months. After one year, approximately 95% of the groups treated with ranibizumab lost fewer than 15 letters from baseline compared with 62% receiving sham injections. The ranibizumab 0.3mg and 0.5mg treatment groups were also more likely to have at least a 15 letter VA gain (25% and 34% respectively) compared with sham injections (5%). Quality of life improvements were also demonstrated with ranibizumab therapy (Kaiser et al., 2007; Rosenfeld et al., 2006).

The ANCHOR trial randomised patients into treatment groups with intravitreal ranibizumab (0.3mg or 0.5mg) and photodynamic therapy with verteporfin (Brown et al., 2006). At one year groups treated with ranibizumab lost fewer than 15 letters from baseline visual acuity in

94% and 96% of cases respectively compared with 64% receiving verteporfin. Furthermore, ranibizumab-treated study eyes gained at least 15 letters in 36% and 40% percent of cases respectively compared with only 6% of study eyes that received photodynamic therapy. Ranibizumab received FDA approval for the treatment of neovascular AMD in 2006 (F.D.A., 2006).

The monthly intravitreal injections that were used in the pivotal clinical trials pose a significant treatment burden to patients, carers, and healthcare providers. Therefore, discontinuous treatment regimens (i.e. intravitreal injections less than every month) have been assessed in clinical trial settings. In the phase 3b PIER clinical trial, eyes were randomised to sham therapy or ranibizumab injections at fixed 3 monthly intervals after an initial loading phase with 3 intravitreal injections at 4 week intervals (Abraham et al., 2010; Regillo et al., 2008). Mean visual gains at 3 months in the 0.3mg and 0.5mg ranibizumab arms were +2.9 and +4.3 letters respectively but these gains were not maintained at 12 months (-1.6 and -0.2 letters) with this reduced frequency fixed treatment regimen.

Treatment regimens based on disease activity were explored. In the Prospective OCT imaging of patients with Neovascular AMD Treated with intraOcular ranibizumab (PrONTO) open-label single-arm study (Lalwani et al., 2009), retreatment was given after 3 loading doses every 4 weeks on an as required basis (pro re nata or "PRN") based on pre-defined OCT and clinical criteria. Mean visual acuity improved over 2 years by 11.1 letters with an average of 9.9 injections, suggesting that OCT-guided PRN treatment regimens could achieve similar visual outcomes to monthly ranibizumab therapy with fewer intravitreal injections. However, the study was limited to 40 study eyes, had no control arm and still required patients to be assessed every 4 weeks.

A prospective trial of the "treat-and-extend" regimen (which aims to inject just before the lesion is about to reactivate) compared with monthly dosing of intravitreal ranibizumab in treatment-naïve neovascular AMD was conducted in 60 patients of whom 50 completed 24-month follow-up at which point mean best-corrected LogMAR letter gains were 10.5 for the monthly and 8.7 for the T&E cohorts (P = .64) (Wyckoff et al., 2017). Over 24 months, the mean number of injections administered was 25.5 and 18.6 for the monthly and T&E cohorts, respectively (P < .001). The trial used an anatomic "no tolerance" approach where even very small amounts of fluid, some at the limit of detection, were treated as evidence of disease activity. Therefore, the mean number of treatments administered to the T&E cohort over 24 months, 18.6, was more than that reported in management regimens using monthly patient visits with PRN retreatment strategies, which ranged from 12 to 14 injections (Martin et al., 2012). Interestingly, over 2 years of the CATT trial, nearly a third of PRN retreatments were withheld from patients because of the presence of reading centre identified fluid on OCT not appreciated by trial investigators (Martin et al., 2012). There is a question whether some degree of subretinal fluid can be tolerated (Razavi et al., 2015).

1.4.3. Bevacizumab

The ABC trial (Tufail et al., 2010) compared 1.25mg intravitreal bevacizumab (three loading injections at six-week intervals followed by further treatment if required at six-week intervals) with standard care at the time (sham or pegaptanib for minimally classic or occult choroidal neovascularisation and verteporfin photodynamic therapy for predominantly classic choroidal neovascularisation) in 126 patients. At the end of the 12-month study, the mean visual acuity gain was 7.0 letters in the bevacizumab group with a median of seven injections compared with a loss of 9.4 letters in the standard care group (P < .001).

Randomised controlled trials comparing intravitreal ranibizumab and bevacizumab found similar efficacy for the treatment of nAMD (Chakravarthy et al., 2013; Martin et al., 2012). The Comparison of AMD Treatment Trial (CATT) in the USA randomly assigned patients with neovascular AMD into one of four treatment groups: intravitreal

bevacizumab (1.25 mg) or ranibizumab (0.5 mg), either as regular monthly injections or PRN (Brown et al., 2009; Martin et al., 2012). At two-years, there was no significant difference in the mean change in visual acuity between the two drugs. Lower visual acuity gains were observed in the PRN groups for both drugs compared with monthly regimens. A similar multicentre randomised controlled trial in the UK named Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN) also concluded that ranibizumab and bevacizumab had similar efficacy and that a reduction in the frequency of retreatment using the PRN regimen resulted in a small loss of efficacy irrespective of the drug employed. The LUCAS multi-centre trial in Norway compared ranibizumab and bevacizumab for neovascular AMD according to a treat-and-extend protocol (Berg et al., 2015). Bevacizumab and ranibizumab had equivalent effects on visual acuity at 1 year (7.9 and 8.2 mean letters gained respectively, $P = .845$) when administered according to a treat-and-extend protocol (mean of 8.9 and 8.0 injections respectively). The visual acuity results at 1 year were comparable to those of other clinical trials with monthly treatment.

The lower cost of off-label bevacizumab compared with licensed intravitreal anti-VEGF agents has contributed to its widespread use. However it is not formally licensed for this indication and care has to be taken that the compounding pharmacies that prepare the intravitreal bevacizumab from larger batches meet stringent quality controls to reduce the risk of endophthalmitis (Goldberg et al., 2013).

1.4.4. Aflibercept

Aflibercept is a soluble fusion protein that, in addition to inhibiting VEGF-A, also binds to VEGF-B (Holash et al., 2002), platelet-derived growth factor and possibly Galectin-1 (Thijssen et al., 2006). The VIEW 1 and 2 phase 3 clinical trials (Heier et al., 2012; Schmidt-Erfurth et al., 2014) enrolled 2457 study eyes. From baseline to week 52, patients received either aflibercept 0.5mg every 4 weeks (0.5Q4), aflibercept 2mg every 4 weeks (2Q4), aflibercept every 8 weeks after three monthly loading injections (2Q8), or 0.5mg intravitreal ranibizumab every 4 weeks (RQ4). The three fixed interval aflibercept groups had similar VA gains compared with fixed interval ranibizumab at 52 weeks, with mean BCVA gains ranging from 8.3 to 9.3 letters. In the second year of the trial a PRN approach was followed in all treatment arms with the maximum treatment interval capped at 12 weeks. The visual acuity gains at 52 weeks in all treatment arms were not fully maintained at week 96 with the mean BCVA gain ranging from 6.6 to 7.9 letters, with the most likely cause being the reduced frequency of intravitreal injections in year 2. Patients received on average 16.5, 16.0, 16.2, and 11.2 injections over 96 weeks and 4.7, 4.1, 4.6, and 4.2 injections during weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. The 2q8 aflibercept group had similar mean visual acuity outcomes to the q4 aflibercept and q4 ranibizumab groups over 96 weeks, but with an average of 5 fewer injections. There was no 2q8 ranibizumab arm in this trial. The incidence of Antiplatelet Trialists' Collaboration-defined arterial thromboembolic events from baseline to week 96 were similar amongst the aflibercept and ranibizumab groups (2.4%–3.8%). Aflibercept was approved by the FDA in November 2011 (F.D.A., 2011).

1.5. The need for real-world evidence in neovascular AMD

It may be contended that the seminal phase 3 randomised controlled trials reporting the outcomes of anti-VEGF therapy for neovascular AMD had good internal validity at the expense of lower external validity. The stringent inclusion and exclusion criteria, relatively small patient numbers, intensive treatment regimens and limited duration of these clinical trials may not necessarily reflect real-world experience. Real-world data was defined by the European Medicine Agency in 2016 as “data collected outside randomised clinical trials usually during normal clinical care” (E.M.A., 2016). The FDA defined real-world evidence as the “evidence derived from aggregation and analysis of real-

Table 2
Strengths and weaknesses of randomised controlled trials and real-world registries.

	Randomised controlled trial	Real-world study
Randomisation	Yes	No
Control arm	Yes	Not necessarily
Sample size	Smaller	Larger
Internal validity	Higher	Lower
External validity	Lower	Higher
Exclusion criteria	Multiple	None or few
Patient comorbidities	Fewer	More
Treatment regimen	Fixed and protocol driven	Variable
Outcomes assessed	Narrow	Can be broader
Cost	More expensive	Less expensive
Duration	Shorter	Longer
Patient retention	Greater	Less

world data elements” (F.D.A., 2016). Table 2 highlights that although real-world studies (e.g. from registries) represent a lower level of certainty on the evidence hierarchy, they can complement findings from randomised controlled trials and have higher external validity since they reflect everyday clinical practice (Black, 1996).

Large-scale population-based observational studies have already shown their value in identifying significant drug adverse events of drugs that were not detected in clinical trials. Real-world evidence has led to subsequent withdrawal of drugs that initially appeared promising in phase 3 clinical trials, such as the lipid lowering medication cerivastatin (Furberg and Pitt, 2001). Post-marketing observational studies, which are carried out after regulatory approval has been given, ensure earlier clinical trials results extend to the general population receiving the new medication. These real-world studies may determine small but significant treatment effects in routine clinical practice by tracking patients for longer and assessing a broader set of endpoints, including safety, quality of life, and long-term effectiveness.

2. Development of global registries to record real-world outcomes in neovascular AMD

2.1. Fight Retinal Blindness registry!

The Fight Retinal Blindness! (FRB!) registry has been tracking outcomes of anti-VEGF treatment for nAMD in Australia, New Zealand and Switzerland since 2007 (Gillies et al., 2014). In order to facilitate accurate, systematic and standardised observation of data across various centres, a practical, web-based tool was developed for data entry. The aim of this interface was to enable monitoring and assessment of different treatment regimens on a large scale while keeping the workload for clinicians at a minimum. Data entry takes approximately 30 s for a new patient and 15 s for a follow-up consultation and is completed during routine clinics. Registered clinicians can input data relating to treatments for patients with neovascular AMD and other retinal diseases to create a user-friendly screenshot of the patient's treatment history. These analytics can be utilised for self-audit and there is the option to pool anonymised data with other departments nationally and internationally using the application.

Publications from FRB! investigators have addressed many clinically relevant issues of treating neovascular AMD in the “real-world”, including optimum treatment regimens (Arnold et al., 2015; Barthelmes et al., 2018; Essex et al., 2016), time to inactivation of choroidal neovascular lesions (Gillies et al., 2015b), the results of switching anti-VEGF therapy (Barthelmes et al., 2016), and long-term outcomes with anti-VEGF therapy (Gillies et al., 2015a). As of February 2017, the FRB! registry included data from approximately 118,000 treatments from about 8000 eyes of 7000 patients with neovascular AMD. Around 3000 patients are currently actively tracked. A number of global sites in UK, Europe, Middle-East and Asia have commenced tracking their real-world outcomes of anti-VEGF therapy for neovascular AMD using this

software platform, offering exciting opportunities for global comparisons of outcomes in the future (Ozturk et al., 2017). Further analyses from FRB! investigators are included in the following sections.

2.2. UK AMD EMR dataset

Medisoft was founded in 1997 by the late Robert Johnston, a Consultant Ophthalmologist and his brother David Johnston, who brought commercial and marketing experience from the pharmaceutical industry. This software evolved over time and uptake increased in the UK, with over 20 ophthalmology departments in England and Northern Ireland contributing real-world data on outcomes of intravitreal anti-VEGF therapy for neovascular AMD. Further collaborations have been developed between University College London Farr Institute of Health Informatics Research and UK ophthalmology departments to extract pseudoanonymised clinical data (> 3.5 million clinic visits), and imaging data (40 + million OCT slices). This has allowed benchmarking of real-world outcomes to set national standards (Liew et al., 2016), development of novel health economic models to guide cost-effectiveness of drugs (Butt et al., 2017), and provided evidence to support funding of treatments currently rationed by the UK National Institute of Clinical Excellence (Lee et al., 2015, 2017b). Further analyses from the UK AMD EMR users group are also included in the following sections.

2.3. European registries

A total of 3470 patients from 274 centres in Germany received intravitreal ranibizumab for neovascular AMD in the observational WAVE study. The initial German guidelines recommended a loading phase of three intravitreal injections at 1-month intervals, followed by a maintenance phase where patients received retreatment if signs of activity were noted. Patients received a mean of 4.34 (SE = 0.05; median = 3.0) ranibizumab injections over 12 months, with negligible change in mean visual acuity from baseline to month 12 (Watson et al., 2017). Following these results, German authorities changed reimbursement and re-injection policy to promote better outcomes.

In the real-life LUMIERE observational study set in France up to 2009, 551 patients received an average of 5.1 intravitreal ranibizumab injections for neovascular AMD with a mean change in VA from baseline to month 12 of +3.2 letters (Cohen et al., 2013). The TWIN Study reviewed clinical outcomes in France between 2010 and 2011 (Souied et al., 2015) in 881 patients, identifying a mean gain in visual acuity of +4.3 letters over 12 months. Significant improvements were documented in the mean interval between diagnosis and treatment initiation in the TWIN study compared with the LUMIERE study (down from 12.6 to 7.7 days; $P < .001$). After induction, hardly any patients were monitored every month in the TWIN study as recommended, although retreatment was more frequent than in the earlier LUMIERE study (mean 5.6 versus 5.1 injections; $P < .001$).

The Swedish Macula Register (SMR) was established in 2003, went online in 2008 and now covers approximately 82% of all patients with neovascular AMD in Sweden (Westborg et al., 2014). In December 2013, the SMR included nearly 15300 patients and 105300 intravitreal treatments. The data in the SMR are from specialised outpatient retinal clinics. The number of intravitreal anti-VEGF injections was reported to be an important factor for treatment outcomes after 1 and 2 years of therapy (Westborg et al., 2017).

The AURA study was funded by Bayer HealthCare Pharmaceuticals AG, Leverkusen, Germany. It was a retrospective, observational, multicentre study of 2227 patients conducted in France, Germany, Italy, Netherlands, UK, Ireland, Canada and Venezuela (Holz et al., 2016). Of the eight countries, five enrolled more than 400 patients (France, Germany, UK, Italy and the Netherlands), hence this is a predominantly European dataset. Mean change in visual acuity score from baseline to years 1 and 2 was +2.4 and + 0.6 letters, respectively. Patients

received a mean of 5.0 and 2.2 injections in the first and second year, respectively. There were substantial differences in visual outcomes and injection frequency between countries. More frequent injections and worse baseline vision were associated with greater improvements in visual acuity. The differences in visual outcomes between countries is likely due to varying constraints within their healthcare systems, including reimbursement, selection of patients for treatment, time until treatment is initiated and the number of injections permitted.

2.4. Development of registries in the USA (IRIS)

The American Academy of Ophthalmology Intelligent Research in Sight (IRIS) registry launched in 2014 has already become the largest American clinical specialty data registry with nearly 50 million patient visits and over 14 million patients (De Fauw et al., 2017). This is in comparison to a prior attempt at a clinical outcomes registry, the National Eye Care Outcomes Network (NEON) launched in 1995, which accumulated only 17,876 patients from 249 participating ophthalmologists over 5 years of operation before its decline (Lum et al., 2002). The key lessons learned from the NEON database were that manual double data entry by practices was untenable and, for the effort to be sustained, data collection had to be a seamless component of workflow. Therefore, the IRIS registry is designed to extract data from the practice's server which contains the electronic medical record (EMR) database using systems integrator software, creating a large central repository of structured data from across diverse EMR systems. Data from the IRIS registry has already been used to characterise treatment patterns of myopic choroidal neovascularisation in the USA (Willis et al., 2017). As of 1st July 2017, 16,737 physicians from 5097 practices are participating in the IRIS registry, contributing over 147 million visits from over 37 million patients. Approximately 6 million anti-VEGF injection episodes have so far been recorded in the IRIS registry (Personal communication, Flora Lum, 5th September 2017). The IRIS registry should provide useful insights in to outcomes of neovascular AMD treated with anti-VEGF agents.

2.5. The LUMINOUS study

LUMINOUS (NCT01318941), a recently-completed, five-year, multicentre, global, observational study, was designed to evaluate the long-term effectiveness, safety, and treatment patterns associated with intravitreal 0.5 mg ranibizumab in clinical practice across all licensed indications (nAMD, diabetic macular oedema, branch and central retinal vein occlusion, and myopic choroidal neovascularisation). This study was initiated in March 2011 and recruited a total of 30,138 patients from 488 sites across 42 countries, of whom 22,717 had nAMD.

A total of 6241 patients with nAMD were treatment-naïve and at baseline the mean age of this cohort was 75.0 years, 54.9% were female, 66.5% were Caucasian and 29.3% were Asian. Of these patients, 2665 (42.7%) had pigment epithelium detachment, 572 (9.2%) had polypoidal choroidal vasculopathy and 246 (3.9%) had retinal angiomatous proliferation (Brand et al., 2017).

There was 12 month visual acuity data available for a total of 3379 treatment-naïve nAMD eyes. The mean baseline VA was 51.9 letters with a mean VA of 55.0 letters at month 12, corresponding to a gain of +3.1 letters (Holz et al., 2017). This improvement in VA was achieved with a mean number of 5.0 ranibizumab injections, which was markedly less than the number administered in pivotal clinical trials, such as ANCHOR (Brown et al., 2006) and MARINA (Rosenfeld et al., 2006). In addition, no new safety signals for ranibizumab were observed during the LUMINOUS study (Holz et al., 2017), despite enrolling patients with more diverse co-morbidities than those generally encountered in randomised controlled trials.

Increased injection frequency was associated with higher 12 month VA gains. Treatment-naïve nAMD eyes receiving ≤ 3 ($n = 537$), 3–6 ($n = 1924$), and > 6 injections ($n = 918$) had mean VA gains of +1.6,

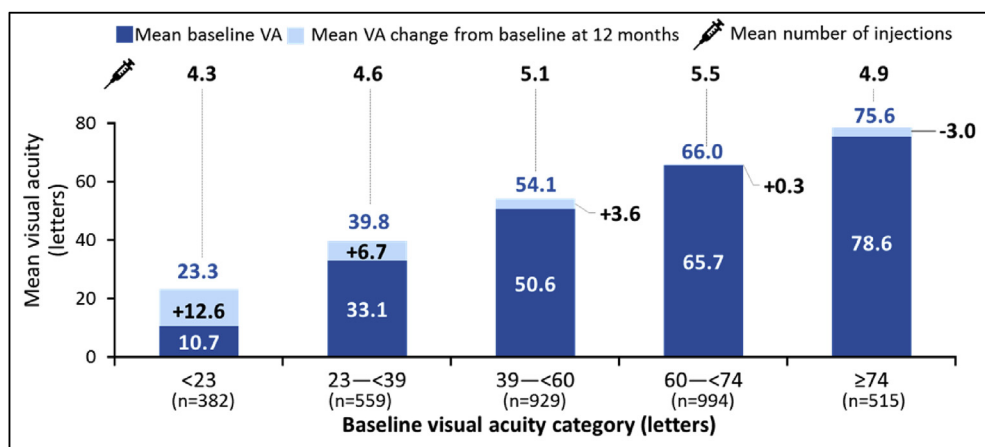


Fig. 1. Visual acuity (VA) outcomes in LogMAR letters at month 12 stratified by baseline VA in treatment-naïve nAMD eyes from the LUMINOUS Study. Reproduced with permission from Wayne Macfadden, Novartis Pharma AG, Basel, Switzerland. n = number of patients with evaluable data at baseline and month 12.

+3.3, and +3.7 letters, respectively. Notably, patients receiving ≥ 10 injections (n = 224, a subset of those patients receiving > 6 injections) had mean VA improvements of +5.7 letters (Holz et al., 2017). Furthermore, month 12 VA changes in these patients stratified by baseline VA of < 23 (n = 382), $23 - < 39$ (n = 559), $39 - < 60$ (n = 929), $60 - < 74$ (n = 994) and ≥ 74 letters (n = 515) were +12.6, +6.7, +3.6, +0.3 and -3.0 letters respectively (Fig. 1) (Holz et al., 2017), indicating that baseline VA should be considered when interpreting visual outcomes.

Ongoing analyses on country level data and patients who were not treatment-naïve upon recruitment to the study are continuing. However, other real-world registries may offer more rapid and comprehensive data collection for some of these outcomes at considerably lower cost.

3. Benchmarking real-world outcomes

3.1. Patient demographics and baseline characteristics

It is important that patient demographics and baseline characteristics are recorded to allow meaningful comparison of outcomes (Rodrigues et al., 2016).

The mean age of patients in seminal clinical trials is on average slightly lower than real-world practice. In a meta-analysis of real-world studies that included over 24000 patients receiving intravitreal ranibizumab for neovascular AMD, the mean age of patients was 78.8 years (95% confidence interval [CI]: 78.0–79.5 years) (Kim et al., 2016) compared with 77 and 76 years respectively in the MARINA and ANCHOR clinical trials of 0.5mg ranibizumab (Brown et al., 2006; Rosenfeld et al., 2006). The average age of patients at entry into the VIEW 1 and 2 aflibercept registration clinical trials was 78 and 74 years respectively (Heier et al., 2012). Younger patients are likely to have less comorbidities.

Gender has not been noted to affect visual outcomes. In the VIEW 1 and 2 clinical trials the proportion of females in the different treatment groups ranged between 50% and 64% without affecting visual outcomes (Heier et al., 2012). A meta-analysis of 42 real-world studies of intravitreal ranibizumab for neovascular AMD found that 63% of patients were female (Kim et al., 2016). Similarly, in a real-world study of intravitreal ranibizumab for neovascular AMD in a well-defined region of rural England, 65% of patients were female (Keenan et al., 2013). There is evidence for greater risk of neovascular AMD in females compared with males even taking into account greater longevity in females (Rudnicka et al., 2012).

Lesion type as defined by fundus fluorescein angiography may affect treatment outcomes. Minimally classic and occult lesions, which are mainly sub-RPE (type 1 lesions) were included in MARINA, which was sham-controlled. Predominantly classic lesions, which are mainly sub-

retinal (type 2 lesions) and responded to photodynamic therapy with verteporfin, were included in ANCHOR (Brown et al., 2006; Rosenfeld et al., 2006). These lesion subtypes were well matched across the different treatment groups of the VIEW 1 and 2 clinical trials (occult 36%–41%, minimally classic 32%–37%, predominantly classic 23%–29%) (Heier et al., 2012). In a real-world study of intravitreal ranibizumab for neovascular AMD in a well-defined region of rural England with a predominantly White population, the proportion of patients with an occult lesion was 51% and lesions with any classic component constituted 36% of all lesions (Keenan et al., 2013). Of the 9350 eyes with data available on their CNV lesion in a global meta-analysis, the majority had an occult lesion (50%), followed by lesions with a classic component (29%) and 18% of lesions unclassified (Kim et al., 2016). The FRB! investigators identified that occult lesions became inactive more slowly than classic lesions without an apparent effect on visual acuity outcomes (Barthelmes et al., 2015; Gillies et al., 2015b). In the above real-world studies, patients from Asia were underrepresented, where there are higher rates of idiopathic polypoidal choroidal vasculopathy reported (Wong et al., 2016).

3.2. Visual acuity outcomes

3.2.1. Baseline visual acuity

Five year real-world outcomes of intravitreal ranibizumab for neovascular AMD in 549 eyes from the FRB! registry mainly set in Australia, stratified by baseline VA are illustrated in Fig. 2 (Gillies et al., 2015a). Eyes with better baseline VA maintain good vision for longer although there is less scope for improvement in VA because of a ceiling effect.

Therefore, baseline VA must be considered when interpreting visual acuity gains over time. The mean baseline VA when intravitreal anti-VEGF therapy is started reflects how well patients can access a service, whereas the visual acuity change over time stratified by baseline VA reflects the quality of the injection service. The FRB! investigators assessed differences in visual outcomes for neovascular AMD treated with intravitreal anti-VEGF between two states in Australia, New South Wales (NSW) and Victoria (VIC) (Gillies et al., 2015). In total, 808 eyes were studied (NSW 540, VIC 227). Mean baseline VA (NSW 60.7, VIC 54.8 LogMAR letters) and mean 24 month VA (NSW 66.3, VIC 62.2 LogMAR letters) for the two states were significantly different ($P < .001$). Eyes received a similar number of injections over 24 months (NSW 12.4, VIC 12.2) with similar injection intervals (NSW 54.9 days, VIC 53.0 days). If the quality of service was simply defined as mean VA gain, then VIC could incorrectly be perceived to have better outcomes. However, the issue appeared to be delay in accessing treatment in some centres in Victoria leading to worse baseline VA. Comparing real-world outcomes allows issues to be highlighted and interventions introduced to improve patient outcomes.

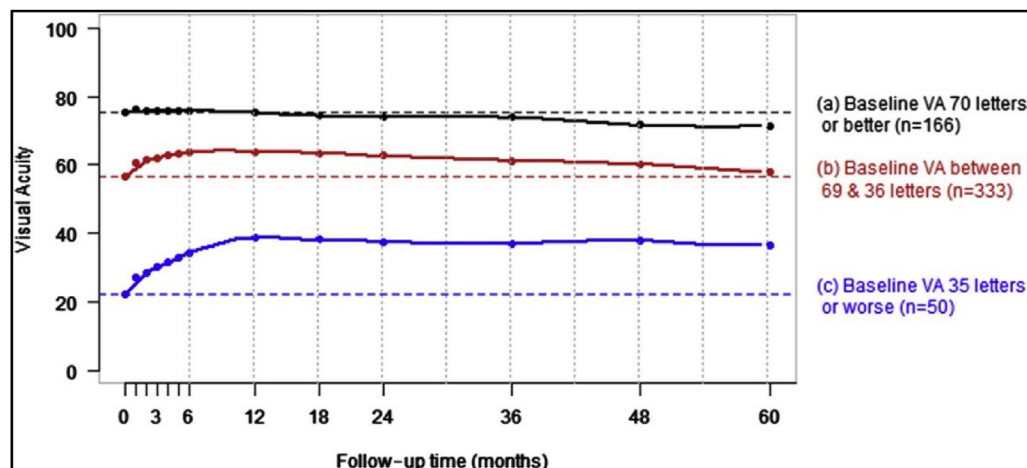


Fig. 2. Reproduced from Long-term outcomes of treatment of neovascular AMD: Data from an observational study (Gillies et al., 2015a). Loess regression curves of visual acuity over 5 years of intravitreal anti-VEGF therapy stratified by baseline visual acuity.

The UK AMD EMR Users group assessed inter-centre variation in VA outcomes with the aim of establishing real-world standards of care (Liew et al., 2016). A prospective multicentre national database study of 13 UK centres that treated patients according to a set protocol (three monthly loading doses followed by PRN retreatment) was performed. A total of 5811 treatment-naïve eyes of 5205 patients were assessed. There was considerable variation in mean baseline VA between centres ranging from 48.9 to 59.9 LogMAR letters. The reasons for this disparity between services warrant further investigation to improve patient outcomes.

3.2.2. Short-term visual outcomes

A meta-analysis of real-world studies of intravitreal ranibizumab for neovascular AMD identified 42 global studies including over 24000 eyes with at least one year follow-up on the search date of 1 May 2015 (Kim et al., 2016). Overall, there was a weighted mean change of +5.0 (95% CI: 3.4 to 6.6), +3.4 (95% CI: 0.9 to 5.8), and +1.1 (95% CI: 25.3 to 7.5) LogMAR letters at 1 year ($n = 24,039$), 2 years ($n = 17,928$), and ≥ 3 years ($n = 13,012$), respectively. Most patients had a baseline VA between 35 and 55 LogMAR letters ($n = 17,464$; 6/60 to 6/24 Snellen equivalent). This was followed by the 55 to 70 LogMAR letters group ($n = 4675$; 6/24 to 6/12 Snellen equivalent) and those with VA > 70 ETDRS letters ($n = 1729$; > 6/12 Snellen equivalent). Patients who commenced treatment with better baseline VA maintained better VA up to at least 36 months. The mean change in VA in the first year of treatment generally increased with the mean number of injections that were administered. The visual outcomes stratified according to treatment regimen are summarised in Table 2 in Section 3.3.

The UK AMD EMR Users group assessed 92,976 ranibizumab injections for 12,951 eyes of 11,135 patients (Tufail et al., 2014). For eyes followed up for at least 3 years, mean VA at baseline was 55 LogMAR letters, at 1 year 57 (+2) letters, at 2 years 56 (+1) letters, and at 3 years 53 (−2) letters using a predominantly prn retreatment approach. The median number of treatments for eyes followed up for at least 3 years in years 1, 2 and 3 was 5, 4, and 4, respectively, and the median number of outpatient visits was 9.2, 8.2, and 8.2, respectively. Baseline VA was related inversely to mean vision gain at 3 months.

The FRB! investigators reported outcomes of intravitreal anti-VEGF therapy, predominantly with ranibizumab, for treatment-naïve eyes with neovascular AMD using a treat-and-extend treatment regimen in routine clinical practice. Data from 1198 eyes from 1011 patients with 24-month follow-up between 2007 and 2012 were included in the analysis. The mean VA increased by +5.3 LogMAR letters from 56.5 letters at baseline to 61.8 letters at 24 months. Mean VA gains improved and number of injections increased with successive years from +2.7 letters for eyes commencing in 2007 after a mean of 9.7 injections in 2 years, to +7.8 letters for eyes commencing in 2012 after a mean of 14.2

injections over 2 years. The proportion of eyes with VA > 6/12 increased from 27% at baseline to 45% after 24 months; the proportion with vision of < 6/60 remained unchanged (13% at baseline and 11% at 24 months). Of the included eyes, 90.5% avoided a vision loss of ≥ 15 letters. There was an overall mean of 13.0 injections over the 24 months, 7.5 injections in the first year and 5.5 in the second year, with a mean of 14.8 clinic visits. These data indicate that eyes managed in routine clinical practice with a treat-and-extend regimen could achieve good visual outcomes while decreasing the burden of treatments and clinic visits (Arnold et al., 2015).

Visual outcomes in treatment-naïve eyes receiving fixed interval intravitreal aflibercept according to the VIEW protocols over 1 year was assessed in routine clinical practice in 16 UK centres (Talks et al., 2016). The mean age at presentation was 80.0 years (median, 81.0 years) and 63.7% were female. During the first year of treatment with aflibercept, 1840 treatment-naïve eyes of 1682 patients received a median of 8 (mean, 7.0) injections at a median of 8 (mean, 7.3) visits. The mean baseline VA was 53.7 LogMAR letters improving to 58.8 letters (+5.1 letter gain) at 1 year. The proportion achieving ≥ 70 letters increased from 16.4% at baseline to 33.7% at 1 year, and 92% avoided moderate visual loss at 1 year. The mean visual acuity gain +5.1 letters at 1 year was comparable to +8.4 letters in the integrated analysis of the VIEW 1 and VIEW 2 studies (Heier et al., 2012). With adequate treatment frequency, real-world outcomes can be comparable with clinical trial outcomes.

A real-world study has reported that the visual benefits achieved with aflibercept in the first year can be maintained in the second year with a treat-and-extend regimen (Eleftheriadou et al., 2017). The fixed dosing protocol of the VIEW study was largely followed in year 1 and then a protocol used by Moorfields Eye Hospital (London) recommended using a treat-and-extend approach in year 2 with a maximum extension of treatment interval of 3 months. Retrospective analysis of 109 consecutive treatment naïve eyes from 102 patients were assessed with data from 94 eyes of 88 (86%) patients available at 2 years. Over the 2 years, these eyes received a median of 12 (mean, 11.4; SD, 4) injections, with mean VA improving from 55.9 (SD, 15) letters at baseline to 61.3 (SD, 16.9) letters (mean VA gain 5.4 letters) at 1 year and to 61.0 (SD, 17.1) letters (mean VA gain 5.1; SD, 14.9 letters) at 2 years. The results suggest that good outcomes can be achieved in the real-world using aflibercept for neovascular AMD with treat-and-extend posology in the second year of treatment after following the VIEW protocol in the first year.

Can a treat-and-extend approach from baseline yield better results? The FRB! investigators reported 24-month outcomes using aflibercept in 136 eyes of 123 patients for neovascular AMD using a treat-and-extend regimen (Barthelmes et al., 2018). Mean (SD) age was 77.2 (7.0) years, 59% were female. Mean (SD) VA increased from 61.4 (17.4)

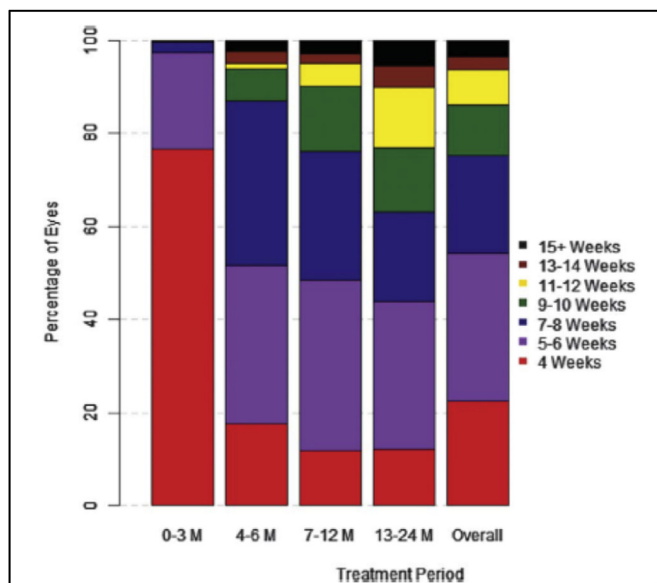


Fig. 3. Percentage of eyes and their mean treatment interval during various periods since beginning aflibercept monotherapy for those eyes which completed 2-year follow-up. Reproduced from Two year outcomes of "treat-and-extend" intravitreal therapy using aflibercept preferentially for neovascular AMD (Barthelmes et al., 2018).

letters at baseline to 67.4 (17.7) letters at 24 months (+6.0 letters [95% CI: 3.3–8.5]; $P < .001$). From baseline to 24 months, the proportion of eyes with visual acuity ≥ 70 letters (6/12) increased (40%–58%, $P < .001$) and the proportion of eyes with visual acuity ≤ 35 letters (6/60) remained the same (10%; $P = .547$). Ninety-eight per cent of eyes starting with visual acuity ≥ 70 letters were able to maintain this up to 24 months. From the first to the second year of treatment, the mean [SD] number of injections (7.8 [2.1] versus 5.7 [2.6]; $P < .001$) and visits (8.7 [1.7] versus 6.5 [2.4]; $P < .001$) decreased for eyes completing 24 months of treatment. Fig. 3 demonstrates that although the mean number of aflibercept injections required over year 1 was similar between the treat-and-extend regimen and the VIEW protocol fixed interval regimen, there can be considerable variation when dealing with individual eyes with some requiring more and some less treatment. When data from 60 eligible eyes that did not complete 2 years follow-up, along with 14 eyes that switched to

ranibizumab, were included using last observation carried forward, the mean change in VA from baseline was +5.6 letters (95% CI: 3.3–7.7).

Comparisons between observational datasets must be done with care. In this case, a good gain of around 5 letters after 12 months of treatment with aflibercept was reported by Talks et al. using the VIEW protocol in the first year. Eleftheriadou et al. confirmed this in another UK population and reported that the mean gain held at 2 years using a treat-and-extend regimen. The FRB! investigators reported a similar mean VA improvement with a treat-and-extend regimen from the start, however the mean pre-treatment VA in their cohort was at least 5 letters greater than the other studies, resulting in better overall outcomes. These better outcomes are at least as likely to be due to earlier intervention in the FRB! cohort as to a superiority of a treat-and-extend regimen over fixed interval dosing in the first year of treatment.

3.2.3. Long-term visual outcomes

Real-world data collection allows long-term results to be obtained that might not be practical with randomised controlled trials. The FRB! investigators analysed the long-term outcomes of treatment-naïve eyes with neovascular AMD that had started treatment with intravitreal anti-VEGF therapy (predominantly ranibizumab) at least 5 years previously. Locally weighted scatterplot smoothing curves (Loess regression curves) were used to display VA results (Fig. 4). The mean follow-up time of all 1212 identified eyes was 53.5 months and 549 (45%) continued attending after 60 months. Mean VA improved from 55.1 to 61.4 letters after 6 months and remained above the mean presenting VA for approximately 5 years. After 7 years, mean VA was 2.6 letters lower than baseline for the 131 eyes still being followed; 40% had VA ≥ 70 (6/12) letters and 18% had VA ≤ 35 letters (6/60). Of those with 6/12 VA before treatment, 60% maintained it after 7 years. The cause of loss ≥ 10 -letters in a subset of eyes were retrospectively analysed: 37% of these were said by the investigators to be due to geographic atrophy affecting the centre of the fovea. A median of 6 injections and 9 visits were recorded over the first 12 months, and then 5 treatments and 7 to 9 visits per annum thereafter through 7 years.

The FRB! results were better than the report from the SEVEN-UP extension study of patients who had participated in ANCHOR or MARINA then HORIZON clinical trials and were subsequently treated in routine clinical practice. These patients had a mean loss of 8.6 letters over 7 years. The main difference between the studies was that patients in the FRB! registry received substantially more injections from the third year (Gillies et al., 2015a; Rofagha et al., 2013). Similarly, The

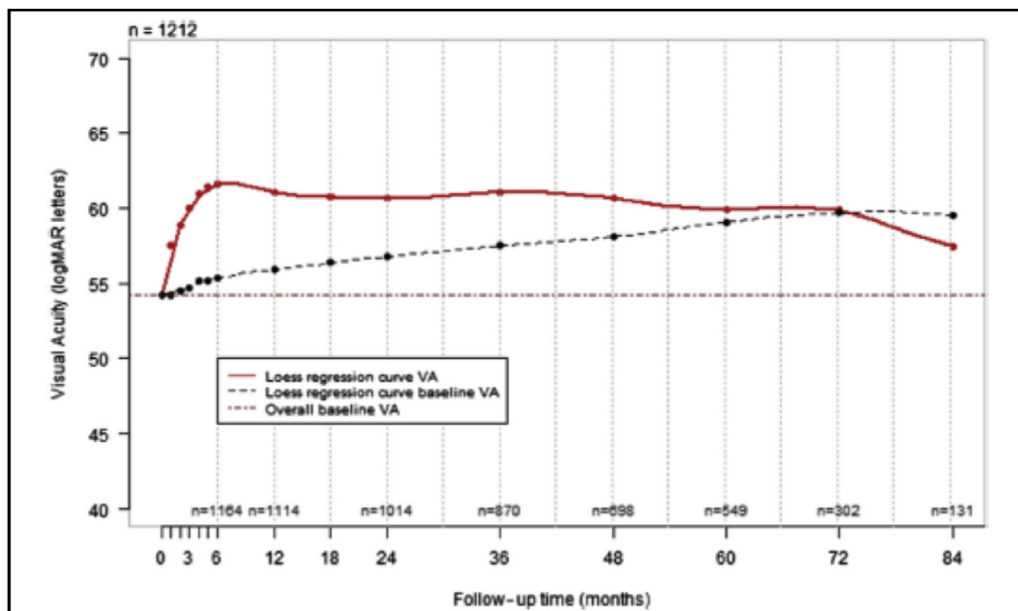


Fig. 4. Reproduced from Long-term outcomes of treatment of neovascular AMD: Data from an observational study (Gillies et al., 2015a). Loess regression curve of mean visual acuity (VA) in LogMAR letters for all 1212 eligible eyes over time. At each time-point, the number of eyes still being followed is displayed above the horizontal axis. The red solid line represents the Loess curve for the VA, and the black dashed line represents the mean baseline VA for those eyes still observed at the marked time-points.

Table 3

Modified from Table 4 in Meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration (Kim et al., 2016). VA = Visual acuity. ΔVA = Change in visual acuity. CI = Confidence Interval.

Treatment Regimen	Baseline VA (95% CI)	ΔVA at 1 year (95% CI)	ΔVA at 2 year (95% CI)	ΔVA at 3 year (95% CI)	Mean Yearly Injections (95% CI)
Overall	53.6 (51.0–56.2)	+5.0 (3.4–6.6) n = 24,039	+3.4 (0.9–5.8) n = 17,928	+1.1 (-5.3 to 7.5) n = 13,012	5.4 (4.6–6.2)
PRN (n = 21,612)	53.0 (50.0–56.0)	+3.5 (2.0–5.0) n = 20,247	+1.3 (-1.6 to 4.2) n = 14,408	-1.9 (-9.8 to 6.0) n = 11,714	4.7 (4.0–5.5)
Treat-and-extend (n = 2566)	52.0 (46.5–57.6)	+8.8 (5.8–11.8) n = 1539	+6.7 (3.2–10.1) n = 2521	+5.4 (-4.1 to 14.9) n = 1298	6.9 (5.6–8.2)

CATT long-term study highlighted an average of 3.3 letters lost 5 years after starting treatment compared with 0.7 letters lost in the FRB! registry (Comparison of Age-related Macular Degeneration Treatments Trials Research et al., 2016; Gillies et al., 2017). These findings suggest that visual acuity at baseline together with treatment regimen and intensity are the most significant influences on long-term visual outcomes.

Aflibercept entered the market later than ranibizumab and therefore less long-term real-world data is available currently but would be expected in the future.

3.2.4. Incidence of sight impairment and blindness

The incidence of sight impairment and blindness in 11,135 treatment-naive patients receiving ranibizumab for neovascular AMD in the UK over 4 years was studied by the UK AMD EMR Users group (Johnston et al., 2016). The cumulative incidence of new sight impairment (VA in better-seeing eye worse than 6/15) and blindness (VA in better seeing-eye worse than 6/60) in patients with treated neovascular AMD in at least 1 eye at years 1–4 after the first injection were 29.6%, 41.0%, 48.7%, and 53.7% for new sight impairment and 5.1%, 8.6%, 12% and 15.6% for new blindness, but with significantly lower rates for patients that started treatment later ($P < .0001$). One reason for the decreasing incidence of sight impairment and blindness in later cohorts was that baseline VA of the worse-seeing eye improved over time as the legacy of absence of anti-VEGF treatment decreased over time. An important limitation of the study was the unknown status of the patients who were censored due to loss of follow-up (see Section 5.2).

From 2000 to 2010 the incidence of legal blindness in Denmark from both neovascular and geographic AMD fell to half the baseline incidence. The bulk of the reduction occurred after the introduction of intravitreal anti-VEGF agents in 2006 (Bloch et al., 2012). Similarly, following the introduction of intravitreal ranibizumab in south-east Scotland, there were annual decreases in the incidence of blindness attributable to neovascular AMD (Boroah et al., 2015). Cases in the south-east Scotland population fell from a peak of 9.1 cases per 100000 in 2006 to a trough of 4.8 cases per 100000 in 2011, a decline of 47% from the peak level.

Whilst effective treatments to reduce the incidence blindness are welcome, it has been suggested that on a population level the beneficial effects of the new treatments for neovascular AMD will be outweighed by the large number of new cases due to the strong anticipated 'ageing' effect in countries such as the UK (Minassian et al., 2011).

3.3. Comparing real-world outcomes with different treatment regimens

The continuous monthly dosing of intravitreal anti-VEGF therapy that was proposed for ranibizumab on the basis of the MARINA and ANCHOR studies proved to be impractical in a real-world setting. As a result, three broad strategies have gained popularity in real-world practice: PRN, treat-and-extend and fixed interval dosing (see Section

1.3). There is the opportunity to compare visual outcomes from observational studies with these different treatment strategies provided baseline characteristics are well matched.

PRN re-treatment approaches were popular in many countries, including the UK. The UK AMD EMR Users group assessed inter-centre variation in VA outcomes with the aim of establishing real-world standards of care for three monthly loading doses followed by PRN retreatment (Liew et al., 2016). A total of 5811 treatment-naive eyes of 5205 patients received a total of 36 206 ranibizumab injections over 12 months. The mean baseline VA between centres varied from 48.9 to 59.9 LogMAR letters. Mean inter-centre VA change from baseline to 12 months varied from +6.9 letters to -0.6 letters (mean of +2.5 letters). The proportion of eyes achieving VA of 70 letters or more varied between 21.9% and 48.7% at 12 months. The median number of injections (visits) at each centre varied from 5 to 8 (9–12), with an overall median of 6 (11). Age, baseline VA, number of injections and number of visits but not gender were associated with variation in these VA outcomes ($P < .01$).

A meta-analysis of global real-world outcomes of over 24000 eyes treated with ranibizumab for neovascular AMD suggested that treat-and-extend regimens were associated with better visual outcomes than PRN regimens, although more injections were required to achieve this (Table 3). Both groups had similar mean baseline visual acuity but there may have been differences in baseline characteristics (Kim et al., 2016).

A similar observation was made comparing PRN treatment in 5 UK centres with a treat-and-extend approach in 4 Australian centres. The study included patients with a diagnosis of neovascular AMD who started treatment with ranibizumab between 2009 and 2014. A total of 647 eyes of 570 patients in Australia and 3187 eyes of 2755 patients in the UK with complete 12-months follow-up were analysed. Baseline patient characteristics were comparable between the two cohorts. After 1 year of treatment, treat-and-extend treated eyes achieved higher mean VA gains (5.0 [95% CI: 3.9–6.1]) than PRN treated eyes (3.0 [95% CI: 2.6–3.5] LogMAR letters); difference in means 2.1 (95% CI: 0.7–3.4), $P < .001$. Over the 12-month follow-up, treat-and-extend treated eyes received a higher mean (+/-SD) number of injections (9.3 ± 2.4) than PRN treated eyes (6.0 ± 2.2) ($P < .0001$). The treat-and-extend cohort had a lower mean (+/-SD) number of clinic visits (10.29 ± 2.90) than the PRN cohort (11.47 ± 2.93) ($p < .0001$). The higher injection frequency in the treat-and-extend cohort likely accounts for the trend towards improved visual outcomes (Johnston et al., 2017).

The UK AMD EMR Users group compared the effectiveness of fixed interval or treat-and-extend aflibercept versus PRN ranibizumab therapy for neovascular AMD (Lee et al., 2017a). They assessed 1-year outcomes in 1884 eyes (942 in each cohort) with groups matched for age, gender, baseline VA and year of starting treatment. At year 1, patients on PRN ranibizumab gained 1.6 LogMAR letters (95% CI: 0.5 to 2.7), while patients on fixed interval or treat-and-extend aflibercept gained 6.1 letters (95% CI: 5.1 to 7.1). The fixed interval or treat-and-extend aflibercept group had significantly more injections compared

with the PRN ranibizumab group (7.0 versus 5.8, $P < .001$) but required fewer clinic visits (10.8 versus 9.0, $P < .001$). The authors commented that the observed VA differences are likely to be related to more frequent injections with aflibercept, suggesting that ranibizumab should also be delivered by fixed dosing or treat-and-extend posology. There was a more pronounced initial rise in visual acuity in the loading phase with aflibercept than ranibizumab which warrants further investigation, preferably controlling for baseline characteristics and number of injections in the first 12 weeks.

TERRA is a real-world observational study being conducted in England and Wales, which quantifies both the resource use and early clinical outcomes of a treat-and-extend regimen of ranibizumab for neovascular AMD. An interim report found that treat-and-extend was compatible with one-stop services, which can be less resource intensive than two-stop (separate assessment and injection) services, and may provide a dosing regimen beneficial to both patients and resource use in UK clinical practice (Yang et al., 2017).

3.4. Comparing real-world outcomes with different anti-VEGF agents

Randomised controlled trials are the preferred method for comparing the efficacy and safety for different interventions for a disease process. However, real-world datasets can provide complementary information especially if the sample sizes are large and inclusion criteria are more representative of the general population. Caution does have to be exercised when interpreting real-world comparisons due to the potential for unmatched baseline characteristics and introduction of selection, performance, detection, attribution and reporting bias. Prospective studies are likely to be more robust than retrospective analyses.

The FRB! Investigators (Gillies et al., 2016) directly compared VA and injection frequency outcomes between eyes receiving ranibizumab or aflibercept for nAMD in routine clinical practice. Treatment-naïve eyes with nAMD that commenced intravitreal ranibizumab or aflibercept between December 1, 2013, and January 31, 2015 were included. Eyes were matched at baseline for VA, age, and CNV size. Eyes that switched or discontinued treatment were included with their last observation carried forward. There were 394 eyes (197 treated with ranibizumab and 197 with aflibercept) from 372 patients identified. Baseline parameters were well matched. The mean (SD) VA of ranibizumab-treated eyes increased from 58.6 (20.3) LogMAR letters at baseline to 62.3 (23.9) (+3.7 [95% CI 1.4–6.1]) letters ($P = .001$), compared with 58.9 (19.2) letters at baseline to 63.1 (21.5) (+4.26 [95% CI 2.0–6.5]) letters ($P < .001$) for eyes receiving aflibercept. The difference in change in crude VA of 0.6 letters between the 2 groups was not statistically significant ($P = .76$), nor was the difference in adjusted mean VA of the 2 groups ($P = .26$). In completers, the mean (SD) numbers of injections (8.1 [2.1] versus 8.0 [2.3]; $P = .27$) and visits (9.6 [3.0] versus 9.5 [3.1]; $P = .15$) did not differ between the groups. The FRB! Investigators identified that VA outcomes at 12 months did not differ between ranibizumab and aflibercept treated eyes in this observational study, nor was a difference in treatment frequency found.

This observation has been replicated in a large retrospective US real-world dataset. Electronic medical records were used to identify ranibizumab or aflibercept-treated nAMD eyes with 12 months follow-up from first prescription. A total of 3350 ranibizumab and 4300 aflibercept treatment-naïve eyes were included. Treatment naïve ranibizumab patients were slightly older than aflibercept patients (47.3% vs 39.9%, respectively, were aged > 85 years) with slightly lower baseline mean (SD) study eye VA [57.5 (21.2) versus 58.5 (20.7); $P = .025$]. At month 12, mean (SD) change from index in VA letter score was -0.30 (14.8) for ranibizumab and -0.19 (14.7) for aflibercept ($P = .81$). Eyes received a similar number of injections during follow-up. The mean (SD) number of ranibizumab and aflibercept injections were 6.70 (2.54) and 7.00 (2.40), respectively ($P < .0001$). Ranibizumab and

aflibercept treatment yielded comparable VA outcomes in nAMD eyes with similar treatment patterns over 12 months in real-world clinical practice (Lotery et al., 2017).

3.5. Systemic safety outcomes

Safety concerns regarding intravitreal anti-VEGF therapies remain unresolved. Systemically delivered anti-VEGF agents are reported to increase blood pressure and risk of thromboembolic events (Kamba and McDonald, 2007). There is a long-running controversy whether intravitreal delivery of anti-VEGF drugs cause the same problems. Recent meta-analyses of systemic cardiovascular adverse events in patients receiving intravitreal anti-VEGF therapy have yielded conflicting results (Avery and Gordon, 2016; Virgili et al., 2014). To date, none of the published randomised controlled trials of anti-VEGF therapy for neovascular AMD had adequate power to rule out small increases in the risk of systemic adverse events that patients might find significant (Esen et al., 2016). Additionally, patients with recent cardiovascular events were excluded from pivotal clinical trials (Brown et al., 2006; Rosenfeld et al., 2006; Schmidt-Erfurth et al., 2014). An effort to evaluate systemic safety issues of these agents is a priority of post-marketing surveillance. In a recent meta-analysis of real-world outcomes of intravitreal ranibizumab for neovascular AMD, the included studies had limited data on systemic safety outcomes (Kim et al., 2016). Linking real-world registries of intravitreal anti-VEGF therapy with national databases of hospital admissions/cardiovascular events could potentially answer these questions (see Section 5.5).

3.6. Ocular safety outcomes

The most feared ocular complication of intravitreal anti-VEGF therapy is endophthalmitis. A meta-analysis of clinical trial and real-world data on infectious endophthalmitis after intravitreal anti-VEGF injections for any indication identified 197 cases out of 350,535 intravitreal anti-VEGF injections (0.056%). The most common organisms isolated were coagulase-negative Staphylococcus (38%) and Streptococcus species (29%). The reported rate of endophthalmitis after intravitreal anti-VEGF injections was low although it is likely this is an underestimate as included studies may not have captured all cases. Streptococcus species represent the causative organism of endophthalmitis after intravitreal VEGF injections at a higher rate than rates reported in the literature for endophthalmitis following most incisional intraocular surgeries. Among patients with endophthalmitis after intravitreal anti-VEGF injection, endophthalmitis caused by Streptococcus species is associated with poorer visual acuity outcomes than endophthalmitis caused by coagulase-negative Staphylococcus and culture-negative cases (Fileta et al., 2014).

The reported rate of endophthalmitis in a meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular AMD was 17 of 66,176 intravitreal injections (0.026%) (Kim et al., 2016). This is likely an underestimate due to incomplete capture of safety outcomes in some real-world registries, this highlights the importance of an agreed standard minimum dataset (see Section 5.1).

The FRB! investigators recommended reporting the “per patient” risk of endophthalmitis with intravitreal anti-VEGF therapy. Some patients in their registry had been treated for up to 10 years and had received over 60 injections. In other circumstances, in which only a single intervention is necessary, such as cataract surgery, it may be adequate just to report endophthalmitis rates “per procedure”. The “per procedure” incidence of infectious endophthalmitis after intravitreal injections of ranibizumab was reported at 0.05% in the MARINA clinical trial, whereas the endophthalmitis rate “per patient” was 1.0% over a 2-year period (Kaiser et al., 2007). In a prospective real-world FRB! study from 2006 to 2016, the incidence of infectious endophthalmitis “per procedure” was 18 out of 88,150 injections (1/4897 injections [0.020%]; 95% CI, 0.012–0.032%) with no difference identified

between different anti-VEGF medications, whereas the rate “per patient” increased over the number of injections from 0.055% after 10 injections to 0.843% after 60 injections (Daïen et al., 2018). However, the analysis did not detect a clinically relevant increase in the risk per injection as the number of injections increased, suggesting the risk of endophthalmitis was linear and not exponential. One quarter of cases with infectious endophthalmitis had lost more than 10 LogMAR letters compared with pre-endophthalmitis visual acuity a year after the adverse event. Much longer follow-up was possible with a real-world study compared with the seminal clinical trials.

The FRB! investigators also assessed the incidence of non-infectious endophthalmitis which developed in 11 of 88,150 injections from 2006 to 2012 (1/8013 injections [0.012%]; 95% CI, 0.006–0.022%). The incidence of non-infectious endophthalmitis was higher for bevacizumab (8/9931, 0.081%) compared with ranibizumab (3/54,776, 0.005%; P = .005) and aflibercept (0/23,425; P = .016), with no significant difference observed between ranibizumab and aflibercept (P = 1.0) (Daïen et al., 2018). The pathophysiology of non-infectious endophthalmitis after anti-VEGF therapy is not fully understood and could involve an immune reaction to the drug itself or impurities gathered in manufacture, preparation, storage or delivery of the agent. Limitations of this analysis include potential under-reporting of unidentified cases and that culture-negative cases of infective endophthalmitis could have been labelled as non-infectious.

Other potential ocular complications of intravitreal anti-VEGF injections include retinal detachment, cataract and raised intraocular pressure. There is the potential to link real-world registries to investigate the risk of these adverse ocular events (see Sections 4.5 and 5.5).

3.7. Quality of life indices

From the patient and payer perspective, a more important treatment outcome than distance visual acuity is quality of life, which reflects not only changes in vision but also the impact of therapy on activities of daily living and emotional well-being. Over 1000 participants involved in the ANCHOR and MARINA Phase III clinical trials of anti-VEGF therapy for neovascular AMD demonstrated a gain in vision-related quality of life (VRQoL) with treatment over 24 months using the 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) (Bressler et al., 2010). However, the NEI-VFQ-25 has been demonstrated to not be psychometrically valid in its native form (Marella et al., 2010).

In contrast, the Impact of Vision Impairment (IVI) profile is a VRQoL instrument that has been shown to be reliable, responsive to interventions and has been rigorously validated using modern psychometric methods, such as Rasch analysis, for different ocular conditions and different levels of visual function (Lamoureux et al., 2007). The IVI consists of 28 items that cover 3 domains: “mobility and independence”, “emotional well-being”, and “reading and accessing information”. The IVI has advantages relating to content, quality and practicality over other validated patient reported outcome measures (PROMs) such as the Metamorphopsia Questionnaire, Macular Disease

Quality of Life, Daily Living Tasks Dependent on Vision, and NEI-VFQ-25 (Rodrigues et al., 2016).

The IVI was used to determine the impact of anti-VEGF treatment as provided in standard medical practice on VRQoL in 169 patients over 12 months at a large public eye hospital in Australia (Finger et al., 2014a). Those who lost > 10 LogMAR letters (11%) reported worse VRQoL at 12 months on the accessing Information and mobility subscales (P = .007 and P = .050, respectively). Conversely, those who gained > 10 LogMAR letters (24%) reported better VRQoL on the accessing information and emotional well-being subscales (P = .009 and P = .008, respectively). Patients who did not experience a significant change in VA reported no change in their VRQoL. In multivariate analyses, only a change in VA but not whether the better or worse eye was treated predicted a change in VRQoL on the accessing Information (P = .004) and the emotional well-being (P = .008) subscales. Future real-world studies would benefit from measurement and standardisation of VR-QoL outcomes (see Section 5.1).

4. Novel observations

4.1. Time to reactivation of neovascular AMD when anti-VEGF treatment is stopped

The seminal clinical trials of intravitreal anti-VEGF therapy for neovascular AMD were 2 years in duration (see Section 1.3). They were not designed to provide evidence on the potential risk of recurrence of disease activity after cessation of anti-VEGF therapy and the impact on visual outcomes.

Initial real-world evidence relating to the risk of disease reactivation was provided in a retrospective review of observational data from a single Australian private practice (Vaze et al., 2014). Eyes in which treatment with intravitreal ranibizumab or bevacizumab was discontinued for more than 3 months during a 3-year period from 2006 to 2009 were analysed. Of 115 eyes from 103 patients, 91% of eyes developed reactivation of neovascular AMD with a significant decline in the mean VA from 58.2 LogMAR letters at the time of last injection to 50.2 letters at the time of recurrence (p < .001, paired t-test). Of the recurrences, 82% were picked up on routine fixed interval examination, while 18% returned earlier with metamorphopsia or decrease in vision. The mean number of injections received before treatment discontinuation was 5.6 (range 3.0–22.0). The median time to disease reactivation after treatment discontinuation for at least 3 months was 33.1 weeks (95% CI: 28.1 to 40.9). Only 9% of eyes did not show any signs of disease reactivation with a mean follow-up of 18 months.

Analysis of a large real-world dataset of over 2000 eyes in the FRB! registry that received intravitreal ranibizumab for neovascular AMD according to a treat-and-extend regimen confirmed a high rate of disease reactivation over time after disease stability had been achieved. As Table 4 illustrates, treatment intervals beyond 12 weeks appear to be associated with an increased risk of disease reactivation, with the risk of reactivation reaching 36.5% per visit at treatment intervals of 20 weeks (Essex et al., 2016). This translated into an increased risk of losing ≥ 15 LogMAR letters with treatment intervals greater than 12 weeks.

Table 4

Frequency and adjusted marginal risk of first reactivation of choroidal neovascularisation at each treatment interval, by treatment interval. CI = confidence interval. Opportunities for reactivation includes visits for all eyes prior to the first reactivation. Modified from Table 3 of Treatment patterns and visual outcomes during the maintenance phase of treat-and-extend therapy for AMD (Essex et al., 2016).

Interval of first reactivation	Opportunities for reactivation	Frequency, n	% Risk per visit (95% CI)	Change in risk from previous level, %
4 weeks	1157	128	9.9 (8.0, 12.3)	0
6 weeks	2100	262	12.1 (10.4, 14.1)	2.2
8 weeks	3019	365	14.5 (12.8, 16.4)	2.4
12 weeks	2650	299	15.3 (13.3, 17.5)	0.8
16 weeks	744	109	20.9 (16.9, 25.5)	5.6
20 weeks	467	126	36.5 (30.5, 43.0)	15.6

Table 5

Change in mean visual acuity (LogMAR letters). Modified from Table 2 of Neovascular age-related macular degeneration database. Report 6: time to retreatment after a pause in therapy. Br J Ophthalmol. (Madhusudhana et al., 2016). TFI, treatment-free interval.

	Mean visual acuity (LogMAR letters)		
	At the beginning of treatment-free period	At the time of retreatment	At first visit after retreatment
TFI 3 months	57.26	54.33	55.43
TFI 6 months	56.90	53.24	54.32
TFI 9 months	56.47	52.29	53.44
TFI 12 months	57.50	53.25	54.27

A large UK observational study analysed the time to re-treatment after a pause in therapy for neovascular AMD in a large dataset of 12951 eyes receiving 92976 intravitreal ranibizumab injections between 2008 and 2012 mainly using a PRN approach (Madhusudhana et al., 2016). Following a treatment free interval (TFI) of 3 months, 6 months, 9 months and 12 months, 77%, 56%, 43% and 34% of these eyes required retreatment after an additional 12 months of follow-up. As Table 5 demonstrates, disease reactivation led to a mean decrease in VA which did not fully recover on restarting treatment.

It might not be advisable to discharge patients or consider them ‘cured’ despite no signs of activity for even after a year of inactivity. Such eyes at the very least require observation and there might be an argument for continued therapy at capped intervals upon reaching disease stability to prevent long-term recurrences in eyes with a good initial response to treatment, especially with longer acting anti-VEGF agents in the pipeline.

4.2. Treating patients with baseline visual acuity better than 6/12 (70 LogMAR letters)

In the UK, the National Institute of Health and Care Excellence (NICE) advises whether drugs are cost-effective for use in the National Health Service. In 2008, NICE only recommended treatment with intravitreal ranibizumab for neovascular AMD if the baseline VA was in the range 6/12–6/96 (NICE, 2008), consistent with the inclusion criteria of the pivotal MARINA and ANCHOR registration clinical trials (Kaiser et al., 2007; Rosenfeld et al., 2006; Brown et al., 2006). In 2014, NICE applied the same baseline VA restrictions to use of intravitreal aflibercept for neovascular AMD (NICE, 2013).

The proportion of eyes with neovascular AMD detected with baseline VA better than 6/12 (70 LogMAR letters) has increased over time, due to increased awareness of the disease and surveillance of high-risk fellow eyes during treatment of the first eye (Barthelmes et al., 2014; Zarranz-Ventura et al., 2014). It seemed reasonable that treating at baseline VA better than 6/12 is more likely to result in a patient retaining driving vision and maintaining a better quality of life (Keenan et al., 2013). It is unlikely that a clinical trial will now be conducted to replicate the ANCHOR and MARINA clinical trial design for study eyes with better than 6/12 vision at baseline, where the control arm received deferred treatment. Real-world registries can provide useful evidence in this context.

The UK AMD EMR Users Group evaluated the efficacy of initiating treatment with ranibizumab for neovascular AMD in eyes with baseline VA better than 6/12 (> 70 LogMAR letters) in routine clinical practice in the UK National Health Service. Some of the commissioning groups in the UK had provided funding to treat patients with better than 6/12 baseline VA. Anonymised structured data were collected from 14 UK centres. The primary outcome was the mean VA at year 1, 2 and 3. A total of 754 of 11 135 patients had baseline VA better than 6/12 and at least 1-year of follow-up. All eyes with baseline VA better than 6/12 maintained superior mean VA than the eyes with baseline VA between

6/12 to 6/24 at all time-points for at least 2 years (globally adjusted p-values < 0.001 in year 1 and 2). Fewer than 50 eyes had baseline VA better than 6/12 at baseline and 3 years follow-up. The authors reported that the significantly better visual outcome in patients who were treated with good baseline VA had implications for future policy regarding funding treatment for nAMD (Lee et al., 2015).

Data can also be evaluated from other countries where arbitrary baseline VA restrictions are not applied. Five year real-world outcomes of intravitreal ranibizumab for neovascular AMD in 549 eyes from the FRB! database mainly set in Australia, stratified by baseline VA are illustrated in Fig. 2 (Gillies et al., 2015a). Eyes with better baseline VA maintain good vision for longer although there is less scope for improvement in VA because of a ceiling effect.

NICE is currently evaluating its guidance regarding intravitreal anti-VEGF treatment for neovascular AMD in the UK for patients presenting with baseline VA better than 6/12. It is important they and other advisory bodies evaluate both clinical trial and real-world evidence to come to decisions in the best interests of patients.

4.3. Second affected eyes had better visual acuity outcomes after anti-VEGF treatment

An analysis of 1207 eyes from 1033 patients with neovascular AMD treated in Gloucestershire, United Kingdom with intravitreal ranibizumab between 2008 and 2012 identified median baseline VA was significantly better for second treated than first treated eyes (66 versus 56 LogMAR letters respectively; $p < .0001$) (Keenan et al., 2013). A slow decline in VA in one eye may go unnoticed if the other eye still has good vision and patients are likely to seek help more quickly and be aware of how to access appropriate healthcare services when the second (better seeing) eye is affected. It is also likely that second eye involvement would be detected earlier during the regular visits required for treatment of the first affected eye.

The UK AMD EMR Users Group identified that 1816 (16.3%) of the total cohort of 11135 patients received intravitreal ranibizumab treatment to the fellow eye between 2008 and 2012 (Zarranz-Ventura et al., 2014). Over 3 years, mean baseline and final VA were 52 LogMAR letters and 51 LogMAR letters for first treated eyes and 62 LogMAR letters and 57 LogMAR letters for second treated eyes. First treated eyes gained more vision most likely due to treatment starting at worse baseline VA, but second treated eyes which had less scope for vision improvement on average maintained better absolute levels of vision. When fellow eyes with baseline VA worse than 6/60 were excluded to restrict analyses to eyes at risk of neovascular AMD, the rate of second eye involvement was 14.0% per year (42% over 3 years) (Zarranz-Ventura et al., 2014). The rate of VA loss after the loading phase was similar in first and second treated eyes (1.5 and 2.5 LogMAR letters/year). The mean number of injections/visits in years 1, 2, and 3 were similar for first and second treated eyes (5.6/8.2, 3.9/8.0, 3.8/8.2 and 5.5/8.7, 3.6/9.4, and 3.8/9.1, respectively).

The FRB! dataset independently corroborated these findings. Of a cohort of 1992 patients, 28% had bilateral disease (Barthelmes et al., 2014). There were 176 participants in which first and second eyes had been diagnosed with neovascular AMD at least 2 months apart with a minimum of 12 months of follow-up data. Mean baseline VA in first affected eyes was 49.7 LogMAR letters. Mean greatest linear dimension in first eyes was 2840 μ m (Q1 1500 μ m, Q3 3500). Median time to diagnosis of the second eye was 427 days after the first eye. At their index visit, second eyes had better VA (mean 61.2 LogMAR letters) and smaller lesion size (mean greatest linear dimension of 2250 μ m). Twelve months after commencing intravitreal anti-VEGF treatment with ranibizumab, first-affected eyes had a mean VA of 56.9 LogMAR letters (mean 7.2 letter improvement compared with the index visit; $P < .001$), whereas second-affected eyes had a mean VA of 65 LogMAR letters (mean 3.8 letter improvement compared with the index visit; $P < .001$). Although a greater mean improvement was observed in first

eyes, their 12-month mean VA was still less than that of the second eye group. Choroidal neovascular lesions were diagnosed by the treating physician as either occult, minimally classic, predominantly classic, or retinal angiomatous proliferation; all other lesion types were combined into a single category. Overall, 64% of patients had the same lesion type in each eye (Cohen kappa = 0.48), indicating fair to good concordance of lesion type between first and second affected eyes (Barthelmes et al., 2014). It should be noted that there is real-world evidence that anti-VEGF therapy for neovascular AMD can improve vision-related quality of life irrespective of whether the worse or better eye is treated (Finger et al., 2014a).

Although not addressed in randomised controlled trials, second eye involvement is common. Hence patient education that second eye involvement may occur and regular checks of the second eye during clinics in which the first affected eye is being treated are strongly recommended to identify changes early and institute treatment promptly. Treatment regimens with long intervals (> 12 weeks) between OCT assessments of the second eye may not be advisable.

4.4. Effect of switching anti-VEGF agents for neovascular AMD

There is debate as to whether switching anti-VEGF agents can offer therapeutic benefit in treating neovascular AMD, particularly if there is persistent disease activity despite treatment. The FRB! investigators examined 12-month outcomes of eyes that received ranibizumab for at least 12 months before switching to aflibercept and followed for at least 12 months after the switch (Barthelmes et al., 2016). A total of 384 eyes were switched from ranibizumab to aflibercept after a mean duration of 39.8 months on the original treatment. The mean VA did not change from the time of switching treatment (63.4, SD 15.9 LogMAR letters) to 12 months later (63.3 LogMAR letters, SD 16.7). While 10% of eyes gained 10 or more letters 12 months after the switch, 13% lost the same amount. The mean number of injections decreased by around one injection in the 12 months after switching ($p < .001$), with a decrease in the proportion of choroidal neovascular membrane lesions that were graded as active. The small proportion (6.9%) of eyes that switched back again to ranibizumab had already lost a mean of 5.2 letters from the first switch to the switch back and continued to lose vision at a similar rate for at least 6 months. The mean VA of eyes that switched treatments from ranibizumab to aflibercept was not different 12 months later, although there was a modest increase in treatment intervals and a somewhat greater proportion of eyes that were graded as inactive after the switch.

A multicentre, national, electronic medical record database study was performed in the UK to assess whether there were visual benefits in switching eyes which had been chronically treated with ranibizumab for neovascular AMD to aflibercept (Lee et al., 2017b). Eyes that had received six continuous monthly ranibizumab injections which were then switched to continuous aflibercept were matched to those that received continuous ranibizumab therapy. Matching was performed in a 2:1 ratio for 1344 patients based on visual acuity 6 months before and at the time of the switch and the number of previous ranibizumab injections. Patients who were switched to aflibercept demonstrated transiently significant improvement in visual acuity that peaked at an increase of 0.9 LogMAR letters 3 months after the switch, whereas control patients continued on ranibizumab treatment showed a steady decline in VA. The VA differences between the groups were small but significant ($P < .05$) at 2, 3, and 5 months after the switch. Beginning at 4 months after the switch, the switch group showed a VA decline similar to the control group. Switching from aflibercept to ranibizumab was not assessed mainly because this did not represent a large group of patients as aflibercept had been introduced to the market more recently. Importantly, the number of intravitreal injections in the period after either switching to aflibercept or continuing with ranibizumab did not have to be the same. Therefore, the transient non-sustained improvement may have been due to the increase in the frequency of

injections that occurred at the time of the switching rather than the superiority of one agent over the other.

Real-world registries can collect long-term outcomes data to assess whether tachyphylaxis is a real phenomenon with intravitreal anti-VEGF therapy. Well conducted randomised controlled trials could address whether combining intravitreal anti-VEGF agents, either concurrently or sequentially, could potentially take advantage of their different mechanisms of action.

4.5. Rate of posterior capsular rupture in eyes with previous intravitreal injections

Posterior capsular rupture (PCR) is a complication of cataract surgery that can be associated with significantly worse visual outcomes (Sparrow et al., 2012). The Royal College of Ophthalmologists of England National Ophthalmology Database study of cataract surgery for cases between 2006 and 2010 reported the mean PCR rate was 1.95% (Day et al., 2015).

The United Kingdom AMD and DR EMR Users Group tested the hypothesis that previous intravitreal therapy is a predictor of increased risk of PCR during cataract surgery (Lee et al., 2016). Anonymised data were extracted for eyes undergoing cataract surgery from 20 UK hospitals using the Medisoft electronic medical records system for cases performed between 2004 and 2014. Data were available on 65836 cataract operations, of which 1935 eyes had received previous intravitreal injections (2.9%). Of these injections, 80% were intravitreal anti-VEGF therapy for neovascular AMD. Univariate regression identified patient age, advanced cataract, junior cataract surgeon grade, and the number of previous intravitreal injections were associated with increased risk of PCR. By considering the number of previous intravitreal injections as a continuous variable and adjusting for other significant independent predictors, the odds ratio for PCR per intravitreal injection was 1.04 ($P = .016$). Repeat analysis considering intravitreal injections as a categorical variable identified 10 or more previous injections were associated with a 2.59 times greater likelihood of PCR ($P = .003$) again after adjusting for other significant independent predictors. Possible explanations include inadvertent crystalline lens capsule trauma and zonular trauma either directly or from local scleral deformation at the time of injection. Identification of cases at higher risk of PCR assists preoperative planning and allows patients to be better informed about potential surgical risks (Lee et al., 2016).

Two independent studies have supported this finding. An increased rate of PCR was identified during cataract surgery in 197 eyes with prior intravitreal injections compared with matched control eyes without prior injections (3% versus 0%, $P = .030$) in a retrospective cohort analysis of cataract surgery procedures performed by experienced surgeons at the Duke Eye Center in North Carolina, USA from 2005 to 2012 (Hahn et al., 2016). An analysis of Moorfields electronic databases identified 62 994 cataract surgery procedures undertaken across its UK Trust sites between 2012 and 2015, with 1035 (1.64%) eyes having received previous intravitreal therapy. Prior intravitreal injection was associated with an increased risk of PCR ($P = .037$) with an odds ratio of 1.66 (Shalchi et al., 2017).

5. Future directions

5.1. Defining a minimum set of standard real-world outcome measures for neovascular AMD

A consensus regarding a standardised set of minimum outcome measures for neovascular AMD was required for healthcare professionals to assess their performance objectively and compare it with others to drive improvements in clinical practice. Such a standardised outcome set might also help patients to make well-informed decisions about their treatment and allow insurers or commissioners to understand the quality and value of care that they are funding. Similar

Table 6 Summary of outcomes recommended in the International Consortium for Health Outcomes Measurement macular degeneration standard set. Modified from Table 2 in Defining a minimum set of standardised patient-centered outcome measures for macular degeneration. Am J Ophthalmol. (Rodrigues et al., 2016). *Outcomes applicable to neovascular age-related macular degeneration only.

	Measure	Details	Timing	Data Source
Visual functioning	Distance visual acuity	Distance visual acuity (best of uncorrected, corrected or pinhole) in the affected eye. Change in distance visual acuity should be calculated from baseline and previous visual acuity assessments.	Each clinical visit	Clinical Data
	Mobility and independence	Brief Impact of Vision Impairment questionnaire	Baseline (prior to treatment) and annually (while on treatment)	Patient reported
Vision-related quality of life	Emotional well-being	Brief Impact of Vision Impairment questionnaire	Baseline (prior to treatment) and annually (while on treatment)	Patient reported
	Reading and accessing information	Brief Impact of Vision Impairment questionnaire	Baseline (prior to treatment) and annually (while on treatment)	Patient reported
Disutility of care	Number of treatments	Documentation of individual treatments received for macular degeneration	Each clinical visit	Clinical or administrative data
	Complications of treatment*	Endophthalmitis: Severe intraocular inflammation within 3 months of last intraocular treatment, due to infectious or non-infectious causes	Each clinical visit	
Disease control	Presence of fluid, oedema, or haemorrhage*	Presence of intraretinal or subretinal fluid or haemorrhage that is attributable to activity of neovascular lesion as determined by the treating clinician. This could be based on clinical examination or imaging.	Each clinical visit	Clinical Data

consensus minimum datasets have been used in other areas of medicine, for example coronary heart disease, to support improvements in global standards (McNamara et al., 2015).

Recommendations from a working group of international experts in AMD outcomes registry development and patient advocates were facilitated by the International Consortium for Health Outcomes Measurement (ICHOM). A modified Delphi technique was employed to drive consensus decisions. Potential outcomes were identified through a review of outcomes collected by existing registries and reported in major clinical trials. Outcomes were refined by the working group and selected based on impact on patients, relationship to good clinical care and feasibility of measurement in routine clinical practice (Rodrigues et al., 2016).

Standardised measurement of the outcomes in Table 6 below were recommended by the ICHOM working group. It was recommended that distance visual acuity readings be measured using a logarithm of the minimal angle of resolution (LogMAR) chart, although other measurement systems may be used and subsequently converted to LogMAR visual acuity. Measuring mean change in visual acuity after starting treatment was recommended because it has become the primary outcome of phase III clinical trials for neovascular AMD. However, observational studies have found that, because of ceiling effects, this may skew results in favour of services that detect the disease and start treatment late, since eyes with worse vision have more to gain compared with eyes starting with good vision, which may not gain anything. Therefore the proportion of eyes with stable vision, good vision (better than 6/12; 70 LogMAR letters), and poor vision (worse than 6/60; 35 LogMAR letters) should also be measured.

Patient reported outcome measures (PROMS) are recorded using the brief Impact of Vision Impairment (IVI) questionnaire. The IVI has been validated specifically in patients with AMD and found to have appropriate content and reliability; it has also undergone Rasch analysis. In practical terms, the IVI is also free to use (for non-commercial purposes) and takes approximately 15 min to complete using paper, computer or touch screen-adapted versions. A guide to scoring and analysis of the IVI is included in the ICHOM Macular Degeneration Standard Set Reference Guide (available at <http://www.ichom.org/medical-conditions/macular-degeneration/>). The developers of the IVI are willing to provide advice on the process of translation and validation if needed.

Using the same methodology, the ICHOM working group recommended recording the following baseline clinical characteristics to enable risk adjustment: age, sex, ethnicity, smoking status, visual acuity in both eyes, type of macular degeneration, presence of geographic atrophy, subretinal fibrosis or pigment epithelial detachment, previous AMD treatment and ocular comorbidities (Rodrigues et al., 2016).

The resultant minimum core dataset is inevitably a compromise between intricate details that may be useful for comparison and the practicalities and burden of data collection in busy clinics. Interested care providers should therefore add additional outcomes to meet their specific requirements. However, we would encourage all centres to collect the minimum dataset described here recommended by the ICHOM working group.

5.2. Developments in statistical analyses to address missing data

Loss to follow-up (LTFU) in longitudinal studies may result in biased estimates if patients who drop out are not appropriately accounted for in the final analysis. The STROBE checklist (STROBE, 2007) for observational studies requires researchers to report and justify their handling of LTFU.

Although investigators strive to limit LTFU, in most instances they fail to achieve complete follow-up of all included patients (Wood et al., 2004). A cut-off of 20% of LTFU is used in Evidence-Based Medicine “Levels of Evidence” (Centre-Evidence-Based-Medicine, 2009) to separate “high” and “low” quality RCTs. As depicted in Table 7, the

Table 7

Examples of loss to follow-up rate in observational studies of anti-VEGF therapy in neovascular age-related macular degeneration.

Endpoint	Loss to follow-up rate	Observational study in neovascular AMD, Country
1 year	17%	(Gupta et al., 2010), USA
	21%	(Hjelmqvist et al., 2011), Sweden
	26%	(Finger et al., 2013), Germany
	34%	(Tufail et al., 2014), UK
2 year	16%	(Abedi et al., 2014), Australia
	28%	(Menghini et al., 2012), Switzerland
	34%	(van Asten et al., 2015), Netherlands
	47%	(Holz et al., 2016), European countries mainly
4 year	49%	(Pushpoth et al., 2012), UK
5 year	54%	(Gillies et al., 2015a), Australia, New Zealand, Switzerland

proportion of patients LTFU in neovascular AMD observational studies ranged from 17 to 34% at 1 year to 49–54% at 4–5 years.

To draw inferences from LTFU data, it is necessary to make some assumptions. A common method of analysis restricts attention to individuals for whom the outcome of interest is observed (complete case analysis). This makes the analysis simple, but the implicit assumption that the excluded individuals do not differ systematically in any way from the included individuals is restrictive and unlikely to be true in many cases (Briggs et al., 2003). Nonetheless, many observational studies of anti VEGF-therapy in nAMD patients have used complete case analysis (Cohen et al., 2013; Finger et al., 2013; Gabai et al., 2014; Heimes et al., 2011; Kumar et al., 2011; Pushpoth et al., 2012). One approach is to look at a matched cohort who completed follow-up and had similar characteristics at the time of LTFU.

A common method used to deal with patients LTFU is to take the last observation carried forward (LOCF), where the latest observed value is carried forward to the end of the study. (Chavan et al., 2014; Frennesson and Nilsson, 2014; Ross et al., 2013; Silva et al., 2013; Wolf and Kampik, 2014; Wykoff et al., 2017). LOCF was initially applied to randomised controlled trials in acute diseases such as infection where the patient's status was expected to improve after treatment initiation. In this case, the LOCF method penalises the group with more LTFU. However, in chronic diseases where the treatment goal is to slow patient decline, LOCF may lead to artificially high rates of treatment benefit in groups with more LTFU (e.g. cognitive decline in dementia) (Molnar et al., 2008). Using LOCF in neovascular AMD presumes that the visual acuity would have been stable from the point of dropout to the study endpoint, which is not always the case (Fig. 5).

Suggested strategies to address missing outcome data in neovascular AMD observational studies include multiple imputation or mixed effect models. Briefly, multiple imputation creates sets of complete datasets, each of which is then analysed using standard statistical techniques and the results pooled. This has several advantages over single imputation methods like LOCF. By pooling results from multiple imputed datasets, it takes into account the inherent uncertainty in the value of the missing data and the variation both within and between imputations (Li et al., 2015). However, its implementation in longitudinal data is not straightforward if visits are at irregular intervals. Mixed-effects regression models for repeated measurements can be used to analyse data without the need to impute missing data and are better suited to data that do not have regular measurement intervals. Such models make use of all observed measurements, including subjects that are LTFU.

There is a need for consensus on the statistical methods used to address LTFU in real-world observational studies. This is particularly important when comparing interventions. Regardless of the statistical technique used to address LTFU, a safe option may be to perform a sensitivity analysis to ensure the validity of outcomes.

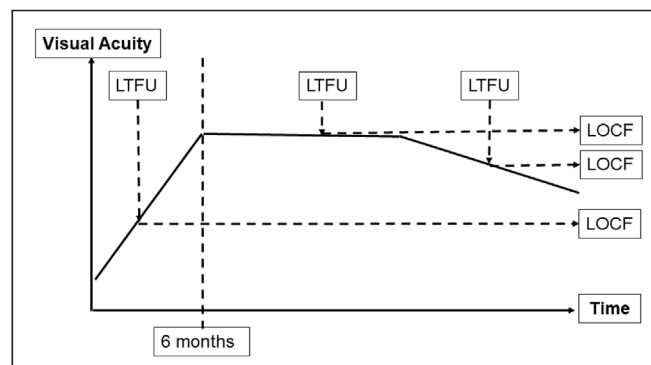


Fig. 5. Effect of last observation carried forward at various times of loss to follow-up in a typical case of neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor drugs. LOCF = Last observation carried forward; LTFU = Lost to follow-up. Using LOCF in age-related macular degeneration presumes that the visual acuity would have been stable from the point of dropout to study endpoint. The general pattern of treated neovascular AMD evolution is a sharp improvement of mean visual acuity in the 6 first months of therapy and then a plateau which either stabilises or slowly decreases over time. LOCF will either overestimate or underestimate the outcomes.

5.3. Mining big data and deep learning

The European Medicine Agency reported that ‘big data’ could be characterised by the ‘5 Vs’: Volume, variety, veracity, velocity and value. (E.M.A., 2016). Big data comprises massive data sets of far greater ‘volume’ and ‘variety’ than traditional data sets and may represent both breadth of data from large numbers of individuals and depth of data on each individual. ‘Veracity’ refers to uncertainty of the quality and robustness of data from different sources. However, the sheer size and variety of big data may overcome a lack of certainty in data sets. Today, data are accumulating at an unprecedented ‘velocity’ and can be transmitted and analysed in real-time. Big data provides ‘value’ by enabling generation of information and knowledge to provide new insights, reveal hidden and rare associations, and increase efficiencies. Sources of real-world data include medico-administrative databases, registries, electronic medical records, surveys and patient generated data, for example from smartphone applications (Salathe et al., 2012; Salathe and Khandelwal, 2011). Some real-world data can be defined as big data when the volume becomes massive.

Optical coherence tomography (OCT) imaging is used to determine disease activity when treating neovascular AMD in routine clinical practice. Within each image are millions of data points. It is possible to link this big data from imaging with clinical trial or registry outcomes using deep learning techniques. For example, the potential for machine learning to predict visual outcomes from structural (OCT imaging) and functional (BCVA) assessments during the initiation phase in 614 patients receiving intravitreal ranibizumab for neovascular AMD in the HARBOR clinical trial has been assessed (Schmidt-Erfurth et al., 2017). Monthly spectral-domain OCT macular volume scans were processed by fully automated computational image analysis. The pre-specified quantitative OCT biomarkers and BCVA measurements at baseline and months 1, 2, and 3 were used to predict BCVA at 12 months using random forest machine learning. The most relevant biomarker for BCVA was the horizontal extension of intraretinal fluid in the foveal region, whereas subretinal fluid and pigment epithelial detachment ranked low. In predicting functional outcomes, the model's accuracy increased in a linear fashion with each month. If only the baseline visit was considered, the accuracy was $R^2 = 0.34$. At month 3, final visual acuity outcomes could be predicted with an accuracy of $R^2 = 0.70$. Whilst yielding interesting results, the random forest machine learning approach used in this analysis was limited in that the biomarkers searched for had to be pre-specified (Schmidt-Erfurth and Waldstein, 2016).

There has been a significant step forward in deep learning techniques with the advent of many-layered neural networks which can be trained to develop convolutional matrices and have the potential to identify novel biomarkers. Convolutional neural networks were inspired by the organisation of the visual cortex. Seminal research conducted by Hubel and Wiesel in the 1960s identified that different individual neurons in the visual cortex fired only in the presence of visual stimuli of edges at certain orientations (Hubel and Wiesel, 1963). For example, some neurons fired when exposed to vertical edges and some when shown horizontal or diagonal edges. They discovered that all of these neurons were organised in a columnar architecture that together produce visual perception. This idea of specialised components inside a system having specific tasks is the basis of convolutional neural networks. Deep learning approaches have progressed due to a number of major leaps forward, not only with convolutional networks, but also the exponential rise of computing power with graphics processing units, non-linear activation functions for solving the vanishing gradient problem, and improved algorithms for stochastic gradient descent (Murphy, 2012). However, often these systems must be exposed to several tens of thousands of examples before this type of deep learning can be used effectively. For example, at the University of Washington, Seattle, investigators have sought to determine if deep learning could be utilised to distinguish normal OCT images from those in patients with any form of AMD (Lee et al., 2017). They selected 52,690 normal macular OCT images and 48,312 AMD macular OCT images and linked them to clinical data from their EMR system. A 21-layer deep neural network was trained to categorise images as either normal or having AMD. Peak sensitivity and specificity with optimal cutoffs were 92.6% and 93.7% respectively. The trained deep learning model learned the OCT features directly from the images themselves without the need for image-specific labels. The investigators identified through occlusion masking that the model was most dependent on pathologic areas to make a diagnosis of AMD. The authors reported that these findings have important implications in utilising OCT in automated screening and the development of computer aided diagnostic tools in the future.

Google DeepMind have collaborated with Moorfields Eye Hospital in London in an exploratory study to investigate whether computer algorithms can detect and classify pathological features on eye imaging, including digital fundus photographs and OCT scans (De Fauw et al., 2017). Approximately 1 million images from the past decade will be assessed. A successful outcome of this exploratory study will provide novel image analysis algorithms to identify and quantify specific pathological features in eye imaging using validated methods and expert clinical consensus. One issue can be the small proportion of misdiagnosed cases in real-world registries. Therefore, additional manual labels will be produced by experts to select images. Google DeepMind will use deep learning techniques to develop the algorithm, including but not limited to convolutional neural networks.

Deep learning approaches could be extended to link a range of multimodal imaging modalities with outcome registries. The UK EMR Users group is planning to link EMR outcomes with information from over 40 million OCT images which should provide new insights into prediction of outcomes in individuals and populations.

5.4. Linking genotypes with outcomes data

Pharmacogenetic associations with anti-VEGF treatments may influence the visual outcomes in neovascular AMD. A prospective cohort study was carried out to determine the association of genetic variants of the VEGF-A gene with the outcome of anti-VEGF treatment in neovascular AMD. From an Australian registry, 201 consecutive patients receiving anti-VEGF injections for neovascular AMD with 12 months follow-up were identified (Abedi et al., 2013). Seven tagged single nucleotide polymorphisms (SNPs) in the VEGF-A gene were selected and examined. In patients with the T allele in tagged SNP rs3025000, there was a significantly better visual outcome at 6 months. The authors

reported visual outcomes of patients harbouring the T allele at SNP rs3025000 were comparable with those of pivotal clinical trials but with fewer injections, perhaps making the treatment more cost-effective in certain subgroups of patients (Abedi et al., 2013).

Evidence on genetic predictors of anti-VEGF treatment response in neovascular AMD has been reviewed. No meta-analysis of results was possible because of the lack of randomised controlled trials, varying treatment regimens, suboptimal reporting and small sample sizes (Finger et al., 2014b). For genetic factors, most evidence to date has been generated for SNPs in complement factor H (CFH) and VEGF-A genes. Just under 50% of the SNPs assessed in the CFH gene and 15% of the SNPs assessed in the VEGF-A gene were found to be associated with visual outcomes or the number of injections required during follow-up. Based on the limited studies conducted thus far, the evidence suggests that the underlying genotype of known AMD risk associated genes (e.g. CFH, VEGF-A and ARMS2/HTRA1) are less important in predicting treatment outcomes than presenting clinical features. Linking large-scale real-world outcome registries with genotyping offers the possibility of targeting therapies for maximum benefit.

Beyond genomics, there is the potential to link metabolomic profiles of patients with treatment outcomes to identify biomarkers and novel therapeutic targets for neovascular AMD (Lambert et al., 2016). Plasma metabolite changes predominantly in the glycerophospholipid pathway have been identified in patients with AMD compared with controls using nuclear magnetic resonance (Lains et al., 2017). Limitations of this study included the cross-sectional design, an almost exclusively White population and no validation cohort. Further work in this area is warranted.

5.5. Linking registries to obtain safety data

Registries may be linked to other databases to allow analysis of systemic safety outcomes. Ng et al. identified patients aged 40 years and over who received treatment with intravitreal anti-VEGF injections for neovascular AMD from 2008 to 2011 at the Singapore National Eye Centre. They used a national record linkage database to identify patients who developed myocardial infarction, stroke and all-cause mortality after the first injection, excluding those with previous myocardial infarction or stroke at baseline from the respective analysis, and compared them with the total Singaporean population. They found that the incidence of myocardial infarction, stroke, and death in this cohort of patients over the age of 40 treated with intravitreal anti-VEGF therapy was low and was not significantly higher than the age-adjusted incidence of these events in the general Singaporean population (Ng et al., 2015). It should be noted that these conclusions cannot be extended to patients who have had previous thromboembolic events as they were excluded from the analysis. There is potential to link databases of intravitreal therapy for neovascular AMD and systemic disease at a national level in countries with comprehensive national registries.

Similarly, registries can be linked to assess ophthalmic safety outcomes. In a clinical trial setting, regular intravitreal anti-VEGF injections have been associated with a sustained rise in intraocular pressure in some patients (Bressler et al., 2015). A Canadian group postulated that sustained elevated intraocular pressure could lead to higher rates of glaucoma surgery. They performed a nested, case-control study and analysed data from large, population-based, linked health databases in British Columbia (Eadie et al., 2017). Study participants included all patients in the Provincial Retinal Diseases Treatment Program who had received intravitreal bevacizumab injections for neovascular AMD between 2009 and 2013. Cases were identified using glaucoma surgical codes. For each case, 10 controls were identified and matched for age, pre-existing glaucoma, and duration of follow-up. The number of intravitreal bevacizumab injections received per year (3 or fewer, 4 to 6, or 7 or more) was determined for both cases and controls. Rate ratios were adjusted for some covariates. There were 74 cases of glaucoma surgery and 740 controls identified, with a mean (SD) age of 81.3 (8.4)

years for cases and 81.4 (7.9) for controls. The adjusted rate ratio of glaucoma surgery among those who received 7 or more injections per year was 2.48 (95% CI, 1.25–4.93). The adjusted rate ratio for those who received 4 to 6 injections per year compared with those who received 3 or fewer was 1.65 (95% CI, 0.84–3.23). The study suggested that 7 or more intravitreal injections of bevacizumab annually is associated with a higher risk of glaucoma surgery. While this is an interesting observation, confounders need to be considered and further studies will be required to provide independent verification before causation can be determined.

Large scale registries have the potential to identify small increases in ocular or systemic risk that randomised controlled trials are not powered to detect. Additionally, patients with comorbidities are more likely to be included in registry studies than clinical trials. Registries also have the benefit of providing long-term follow-up to identify late adverse events.

5.6. Use of real-world registries by regulatory authorities as an alternative to phase 4 trials for new drugs

The number of therapies for neovascular AMD will increase in the future with many new drugs with different modes of action currently in phase I, II and III clinical trials (Pecen and Kaiser, 2015). Real-world outcomes studies can be used by regulatory authorities to assess the generalisability of clinical trial results. Large-scale population-based observational studies facilitate the assessment of efficacy, safety and resource utilisation in a real-world setting. Large real-world observational data sets can be accumulated more rapidly and in a less expensive way than traditional phase 4 clinical trials. Also, the impact of multiple variables can be assessed, which would otherwise be costly and cumbersome if tested for individually and, as demonstrated in section 4 of this review, may allow for novel interactions to be identified. There is the potential to use real-world outcomes to guide remuneration of high cost drugs in the future.

The FDA has access to several big data sources, in particular from the Sentinel Initiative (FDA's electronic system for monitoring safety of medicines) and the Centers for Medicare and Medicaid Services (CMS, payer systems), which together comprise health data for over 200 million people. The FDA intends to publish guidelines on use of real-world data in regulatory submissions (Sherman et al., 2016). They caution that “the confluence of large data sets of uncertain quality and provenance, the facile analytic tools that can be used by non-experts, and a shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions” (Sherman et al., 2016). They report that it is important to distinguish two key elements of real-world evidence. The first is the setting in which evidence is generated, which includes the population defined by the data source as well as the specific methods used to collect and curate the data on that population. The second is the methodologic approach used to conduct the research (Sherman et al., 2016).

Author contribution

Hemal Mehta 50%, Adnan Tufail 5%, Vincent Daien 5%, Aaron Lee 5%, Vuong Nguyen 5%, Mehmet Ozturk 5%, Daniel Barthelmes 5%, Mark C. Gillies 20%.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.preteyeres.2017.12.002>.

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Conflicts of interest

Potential conflicts of interest outside of this work are listed in the attached ICMJE disclosure of potential conflict of interest forms.

References

- 1982. Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. *Arch Ophthalmol* 100, 912–918.
- 1991. Laser photocoagulation of subfoveal recurrent neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. *Macular Photocoagulation Study Group. Arch Ophthalmol* 109, 1232–1241.
- 1993. Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. *Macular Photocoagulation Study Group. Arch Ophthalmol* 111, 1189–1199.
- Abedi, F., Wickremasinghe, S., Richardson, A.J., Makalic, E., Schmidt, D.F., Sandhu, S.S., Baird, P.N., Guymer, R.H., 2013. Variants in the VEGFA gene and treatment outcome after anti-VEGF treatment for neovascular age-related macular degeneration. *Ophthalmology* 120, 115–121.
- Abedi, F., Wickremasinghe, S., Islam, A.F., Inglis, K.M., Guymer, R.H., 2014. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. *Retina* 34, 1531–1538.
- Abraham, P., Yue, H., Wilson, L., 2010. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *Am. J. Ophthalmol.* 150, e311 315–324.
- Aiello, L.P., Avery, R.L., Arrigg, P.G., Keyt, B.A., Jampel, H.D., Shah, S.T., Pasquale, L.R., Thieme, H., Iwamoto, M.A., Park, J.E., 1994. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N. Engl. J. Med.* 331, 1480–1487.
- Arnold, J.J., Campaign, A., Barthelmes, D., Simpson, J.M., Guymer, R.H., Hunyor, A.P., McAllister, I.L., Essex, R.W., Morlet, N., Gillies, M.C., Fight Retinal Blindness Study, G, 2015. Two-year outcomes of “treat and extend” intravitreal therapy for neovascular age-related macular degeneration. *Ophthalmology* 122, 1212–1219.
- Avery, R.L., Gordon, G.M., 2016. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol.* 134, 21–29.
- Avery, R.L., Pieramici, D.J., Rabena, M.D., Castellarin, A.A., Nasir, M.A., Giust, M.J., 2006. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 113, e365 363–372.
- Bailey, I.L., Lovie, J.E., 1976. New design principles for visual acuity letter charts. *Am. J. Optom. Physiol. Optic* 53, 740–745.
- Barthelmes, D., Walton, R.J., Arnold, J.J., McAllister, I.L., Simpson, J.M., Campaign, A., Hunyor, A.P., Guymer, R., Essex, R.W., Morlet, N., Gillies, M.C., Fight Retinal Blindness! Project, I, 2014. Intravitreal therapy in bilateral neovascular age-related macular degeneration. *Ophthalmology* 121, 2073–2074.
- Barthelmes, D., Walton, R., Campaign, A.E., Simpson, J.M., Arnold, J.J., McAllister, I.L., Guymer, R.H., Hunyor, A.P., Essex, R.W., Morlet, N., Gillies, M.C., Fight Retinal Blindness! Project, I, 2015. Outcomes of persistently active neovascular age-related macular degeneration treated with VEGF inhibitors: observational study data. *Br. J. Ophthalmol.* 99, 359–364.
- Barthelmes, D., Campaign, A., Nguyen, P., Arnold, J.J., McAllister, I.L., Simpson, J.M., Hunyor, A.P., Guymer, R., Essex, R.W., Morlet, N., Gillies, M.C., Fight Retinal Blindness! Project, I, 2016. Effects of switching from ranibizumab to aflibercept in eyes with exudative age-related macular degeneration. *Br. J. Ophthalmol.* 100, 1640–1645.
- Barthelmes, D., Nguyen, V., Daien, V., Campaign, A., Walton, R., Guymer, R., Morlet, N., Hunyor, A.P., Essex, R.W., Arnold, J.J., Gillies, M.C., Fight Retinal Blindness Study, G, 2018 Jan. Two year outcomes of “treat and extend” intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. *Retina* 38 (1), 20–28. <http://dx.doi.org/10.1097/IAE.0000000000001496>.
- Berg, K., Pedersen, T.R., Sandvik, L., Bragadottir, R., 2015. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology* 122, 146–152.
- Black, N., 1996. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 312, 1215–1218.
- Bloch, S.B., Larsen, M., Munch, I.C., 2012. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am. J. Ophthalmol.* 153, e202

- 209–213.
- Borooah, S., Jeganathan, V.S., Ambrecht, A.M., Oladiwura, D., Gavin, M., Dhillon, B., Cackett, P., 2015. Long-term visual outcomes of intravitreal ranibizumab treatment for wet age-related macular degeneration and effect on blindness rates in south-east Scotland. *Eye (Lond)* 29, 1156–1161.
- Bourne, R.R., Stevens, G.A., White, R.A., Smith, J.L., Flaxman, S.R., Price, H., Jonas, J.B., Keeffe, J., Leasher, J., Naidoo, K., Pesudovs, K., Resnikoff, S., Taylor, H.R., Vision Loss Expert, G., 2013. Causes of vision loss worldwide, 1990–2010: a systematic analysis. *Lancet Glob. Health* 1, e339–349.
- Brand, C., Mitchell, P., Figueroa, M.S., Lacey, S., Macfadden, W., Group, L.S., 2017. Baseline characteristics of 30,000 patients from the final analysis of the real-world LUMINOUS study. In: 17th EURETINA Congress, Barcelona, Spain.
- Bressler, N.M., 2002. Early detection and treatment of neovascular age-related macular degeneration. *J. Am. Board Fam. Pract.* 15, 142–152.
- Bressler, N.M., 2004. Age-related macular degeneration is the leading cause of blindness. *JAMA* 291, 1900–1901.
- Bressler, N.M., Chang, T.S., Suner, I.J., Fine, J.T., Dolan, C.M., Ward, J., Ianchulev, T., Marina, Groups, A.R., 2010. Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. *Ophthalmology* 117, e744 747–756.
- Bressler, S.B., Almukhtar, T., Bhorade, A., Bressler, N.M., Glassman, A.R., Huang, S.S., Jampol, L.M., Kim, J.E., Melia, M., Diabetic Retinopathy Clinical Research Network, I., 2015. Repeated intravitreal ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. *JAMA Ophthalmol* 133, 589–597.
- Briggs, A., Clark, T., Wolstenholme, J., Clarke, P., 2003. Missing... presumed at random: cost-analysis of incomplete data. *Health Econ.* 12, 377–392.
- Brown, D.M., Kaiser, P.K., Michels, M., Soubrane, G., Heier, J.S., Kim, R.Y., Sy, J.P., Schneider, S., Group, A.S., 2006. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N. Engl. J. Med.* 355, 1432–1444.
- Brown, D.M., Michels, M., Kaiser, P.K., Heier, J.S., Sy, J.P., Ianchulev, T., Group, A.S., 2009. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 116, e55 57–65.
- Butt, T., Tufail, A., Rubin, G., 2017. Health state utility values for age-related macular degeneration: review and advice. *Appl. Health Econ. Health Pol.* 15, 23–32.
- Centre-Evidence-Based-Medicine, 2009. Oxford Centre for Evidence-based Medicine – Levels of Evidence. (March 2009).
- Chakravarthy, U., Harding, S.P., Rogers, C.A., Downes, S.M., Lotery, A.J., Culliford, L.A., Reeves, B.C., investigators, I.S., 2013. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet* 382, 1258–1267.
- Chavan, R., Panneerselvam, S., Adhana, P., Narendran, N., Yang, Y., 2014. Bilateral visual outcomes and service utilization of patients treated for 3 years with ranibizumab for neovascular age-related macular degeneration. *Clin. Ophthalmol.* 8, 717–723.
- Cohen, S.Y., Mimoun, G., Oubraham, H., Zourani, A., Malbrel, C., Quere, S., Schneider, V., Group, L.S., 2013. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina* 33, 474–481.
- Comparison of Age-related Macular Degeneration Treatments Trials Research, G., Maguire, M.G., Martin, D.F., Ying, G.S., Jaffe, G.J., Daniel, E., Grunwald, J.E., Toth, C.A., Ferris, F.L., Fine 3rd, S.L., 2016. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 123, 1751–1761.
- Daien, V., Nguyen, V., Essex, R.W., Morlet, N., Barthelmes, D., Gillies, M.C., Fight Retinal Blindness! Study, G., 2018 Jan. Incidence and outcomes of infectious and non-infectious endophthalmitis after intravitreal injections for age-related macular degeneration. *Ophthalmology* 125 (1), 66–74. <http://dx.doi.org/10.1016/j.ophtha.2017.07.005>. Epub 2017 Aug 8.
- Day, A.C., Donachie, P.H., Sparrow, J.M., Johnston, R.L., Royal College of Ophthalmologists' National Ophthalmology, D., 2015. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. *Eye (Lond)* 29, 552–560.
- De Fauw, J., Keane, P., Tomasev, N., 2017. Automated Analysis of Retinal Imaging Using Machine Learning Techniques for Computer Vision F1000Research, vol. 5. pp. 1573.
- Eadie, B.D., Etmann, M., Carleton, B.C., Maberley, D.A., Mikelberg, F.S., 2017. Association of repeated intravitreal bevacizumab injections with risk for glaucoma surgery. *JAMA Ophthalmol.* 135, 363–368.
- Eleftheriadou, M., Vazquez-Alfageme, C., Citu, C.M., Crosby-Nwaobi, R., Sivaprasad, S., Hykin, P., Hamilton, R.D., Patel, P.J., 2017. Long-term outcomes of aflibercept treatment for neovascular age-related macular degeneration in a clinical setting. *Am. J. Ophthalmol.* 174, 160–168.
- E.M.A., 2016. European Medicines Agency. Workshop on Identifying Opportunities for “big Data” in Medicines Development and Regulatory Science.
- Esen, F., Alhan, O., Kuru, P., Sahin, O., 2016. Safety assessment and power analyses in published anti-vascular endothelial growth factor randomized controlled trials. *Am. J. Ophthalmol.* 169, 68–72.
- Essex, R.W., Nguyen, V., Walton, R., Arnold, J.J., McAllister, I.L., Guymer, R.H., Morlet, N., Young, S., Barthelmes, D., Gillies, M.C., Fight Retinal Blindness Study, G., 2016. Treatment Patterns and Visual Outcomes during the Maintenance Phase of Treat-and-Extend Therapy for Age-Related Macular Degeneration. *Ophthalmology* 123, 2393–2400.
- Evans, J.R., Sivagnanavel, V., Chong, V., 2010. Radiotherapy for neovascular age-related macular degeneration. *Cochrane Database Syst. Rev.*, CD004004.
- Falkenstein, I.A., Cochran, D.E., Azen, S.P., Dustin, L., Tammewar, A.M., Kozak, I., Freeman, W.R., 2008. Comparison of visual acuity in macular degeneration patients measured with snellen and early treatment diabetic retinopathy study charts. *Ophthalmology* 115, 319–323.
- F.D.A., 2005. Macugen (Pegaptanib Sodium) Injection Drug Approval Package. U.S. Food and Drug Administration.
- F.D.A., 2006. FDA News Release (2006): FDA Treatment for Wet Age-related Macular Degeneration.
- F.D.A., 2011. US Food. Drug Administration. FDA News Release (2011): FDA Approves Eylea for Eye Disorder in Older People.
- F.D.A., 2016. Use of Real-world Evidence to Support Regulatory Decision-making for Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff.
- Ferrara, N., Henzel, W.J., 1989. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem. Biophys. Res. Commun.* 161, 851–858.
- Ferris 3rd, F.L., Kassoff, A., Bresnick, G.H., Bailey, I., 1982. New visual acuity charts for clinical research. *Am. J. Ophthalmol.* 94, 91–96.
- Fileta, J.B., Scott, I.U., Flynn Jr., H.W., 2014. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmic Surg. Laser. Imag. Retina* 45, 143–149.
- Finger, R.P., Wiedemann, P., Blumhagen, F., Pohl, K., Holz, F.G., 2013. Treatment patterns, visual acuity and quality-of-life outcomes of the WAVE study - a non-interventional study of ranibizumab treatment for neovascular age-related macular degeneration in Germany. *Acta Ophthalmol.* 91, 540–546.
- Finger, R.P., Guymer, R.H., Gillies, M.C., Keeffe, J.E., 2014a. The impact of anti-vascular endothelial growth factor treatment on quality of life in neovascular age-related macular degeneration. *Ophthalmology* 121, 1246–1251.
- Finger, R.P., Wickremasinghe, S.S., Baird, P.N., Guymer, R.H., 2014b. Predictors of anti-VEGF treatment response in neovascular age-related macular degeneration. *Surv. Ophthalmol.* 59, 1–18.
- Frennesson, C.L., Nilsson, S.E., 2014. A three-year follow-up of ranibizumab treatment of exudative AMD: impact on the outcome of carrying forward the last acuity observation in drop-outs. *Acta Ophthalmol.* 92, 216–220.
- Furberg, C.D., Pitt, B., 2001. Withdrawal of cerivastatin from the world market. *Curr. Contr. Trials Cardiovasc. Med.* 2, 205–207.
- Gabai, A., Veritti, D., Lanzetta, P., 2014. One-year outcome of ranibizumab for neovascular age-related macular degeneration: a thorough analysis in a real-world clinical setting. *Eur. J. Ophthalmol.* 24, 396–401.
- Gass, J.D., Agarwal, A., Lavina, A.M., Tawansy, K.A., 2003. Focal inner retinal hemorrhages in patients with drusen: an early sign of occult choroidal neovascularization and chorioretinal anastomosis. *Retina* 23, 741–751.
- Gillies, M.C., Simpson, J.M., Luo, W., Penfold, P., Hunyor, A.B., Chua, W., Mitchell, P., Billson, F., 2003. A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. *Arch. Ophthalmol.* 121, 667–673.
- Gillies, M.C., Walton, R., Liong, J., Arnold, J.J., McAllister, I., Morlet, N., Hunyor, A., Guymer, R., Keeffe, J., Essex, R., Herrera-Bond, A., Glastonbury, B., Simpson, J.M., Barthelmes, D., 2014. Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. *Retina* 34, 188–195.
- Gillies, M.C.A., Simpson, J., Hunyor, A., Arnold, J., Guymer, R., McAllister, I., Essex, R., Morlet, N., Barthelmes, D., 2015. Outcome and management differences between New South Wales and Victoria for treatment of age-related macular degeneration with anti-VEGF injections. *Clin. Exp. Ophthalmol.* 43, 108–109.
- Gillies, M.C., Campaign, A., Barthelmes, D., Simpson, J.M., Arnold, J.J., Guymer, R.H., McAllister, I.L., Essex, R.W., Morlet, N., Hunyor, A.P., Fight Retinal Blindness Study, G., 2015. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology* 122, 1837–1845.
- Gillies, M.C., Campaign, A., Walton, R., Simpson, J.M., Arnold, J.J., Guymer, R.H., McAllister, I.L., Hunyor, A.P., Essex, R.W., Morlet, N., Barthelmes, D., Fight Retinal Blindness Study, G., 2015. Time to initial clinician-reported inactivation of neovascular age-related macular degeneration treated primarily with ranibizumab. *Ophthalmology* 122, e581 589–594.
- Gillies, M.C., Nguyen, V., Daien, V., Arnold, J.J., Morlet, N., Barthelmes, D., 2016. Twelve-month outcomes of ranibizumab vs. Aflibercept for neovascular age-related macular degeneration: data from an observational study. *Ophthalmology* 123, 2545–2553.
- Gillies, M.C., Daien, V., Nguyen, V., Barthelmes, D., 2017. Re: comparison of Age-Related Macular Degeneration Treatments Trials (CAIT) Research Group, et al.: five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials (Ophthalmology 2016;123:1751-1761). *Ophthalmology* 124, e31–e32.
- Goldberg, R.A., Flynn Jr., H.W., Miller, D., Gonzalez, S., Isom, R.F., 2013. Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: one-year outcomes and investigative results. *Ophthalmology* 120, 1448–1453.
- Gragoudas, E.S., Adamis, A.P., Cunningham, E.T., Feinsod, M., Guyer, D.R., Group, V.I.S.i.O.N.C.T., 2004. Pegaptanib for neovascular age-related macular degeneration. *N. Engl. J. Med.* 351, 2805–2816.
- Gupta, O.P., Shienbaum, G., Patel, A.H., Fecarotta, C., Kaiser, R.S., Regillo, C.D., 2010. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 117, 2134–2140.
- Hahn, P., Jiramongkolchai, K., Stinnett, S., Daluvoy, M., Kim, T., 2016. Rate of intraoperative complications during cataract surgery following intravitreal injections. *Eye (Lond)* 30, 1101–1109.
- Hawkins, B.S., Bressler, N.M., Miskala, P.H., Bressler, S.B., Holekamp, N.M., Marsh, M.J., Redford, M., Schwartz, S.D., Sternberg Jr., P., Thomas, M.A., Wilson, D.J.,

- Submacular Surgery Trials Research, G. 2004. Surgery for subfoveal choroidal neovascularization in age-related macular degeneration: ophthalmic findings: SST report no. 11. *Ophthalmology* 111, 1967–1980.
- Heier, J.S., Brown, D.M., Chong, V., Korobelnik, J.F., Kaiser, P.K., Nguyen, Q.D., Kirchhof, B., Ho, A., Ogura, Y., Yancopoulos, G.D., Stahl, N., Vitti, R., Berliner, A.J., Soo, Y., Anderesi, M., Groetzsch, G., Sommerauer, B., Sandbrink, R., Simader, C., Schmidt-Erfurth, U., View, Groups, V.S. 2012. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 119, 2537–2548.
- Heimes, B., Lommatzsch, A., Zeimer, M., Gutfleis, M., Spital, G., Dietzel, M., Pauleikhoff, D., 2011. Long-term visual course after anti-VEGF therapy for exudative AMD in clinical practice evaluation of the German reinjection scheme. *Graefes Arch. Clin. Exp. Ophthalmol.* 249, 639–644.
- Hjelmqvist, L., Lindberg, C., Kanulf, P., Dahlgren, H., Johansson, I., Siwert, A., 2011. One-year outcomes using ranibizumab for neovascular age-related macular degeneration: results of a prospective and retrospective observational multicentre study. *J. Ophthalmol.* 2011, 405724.
- Holash, J., Davis, S., Papadopoulos, N., Croll, S.D., Ho, L., Russell, M., Boland, P., Leidich, R., Hylton, D., Burova, E., Ioffe, E., Huang, T., Radziejewski, C., Bailey, K., Fandl, J.P., Daly, T., Wiegand, S.J., Yancopoulos, G.D., Rudge, J.S., 2002. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc. Natl. Acad. Sci. U.S.A.* 99, 11393–11398.
- Holmgren, L., O'Reilly, M.S., Folkman, J., 1995. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat. Med.* 1, 149–153.
- Holz, F.G., Tadayoni, R., Beatty, S., Berger, A., Cereda, M.G., Hykin, P., Staurenghi, G., Wittrop-Jensen, K., Altmark, A., Nilsson, J., Kim, K., Sivaprasad, S., 2016. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br. J. Ophthalmol.* 100, 1623–1628.
- Holz, F., Souied, E., Tuli, R., Lacey, S., Macfadden, W., Group, L.S., 2017. Effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration: twelve-month results from the final analysis of the real-world LUMINOUS study. In: 17th EURETINA Congress, Barcelona, Spain.
- Hubel, D.H., Wiesel, T.N., 1963. Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *J. Neurophysiol.* 26, 994–1002.
- Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., Berlin, J., Baron, A., Griffing, S., Holmgren, E., Ferrara, N., Fyfe, G., Rogers, B., Ross, R., Kabbinavar, F., 2004. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 350, 2335–2342.
- Jager, R.D., Mieler, W.F., Miller, J.W., 2008. Age-related macular degeneration. *N. Engl. J. Med.* 358, 2606–2617.
- Johnston, R.L., Lee, A.Y., Buckle, M., Antcliff, R., Bailey, C., McKibbin, M., Chakravarthy, U., Tufail, A., Group, U.A.E.U., 2016. UK age-related macular degeneration electronic medical record system (AMD EMR) users group report IV: incidence of blindness and sight impairment in ranibizumab-treated patients. *Ophthalmology* 123, 2386–2392.
- Johnston, R.L., Carius, H.J., Skelly, A., Ferreira, A., Milnes, F., Mitchell, P., 2017. A retrospective study of ranibizumab treatment regimens for neovascular age-related macular degeneration (nAMD) in Australia and the United Kingdom. *Adv. Ther.* 34, 703–712.
- Kaiser, P.K., Blodi, B.A., Shapiro, H., Acharya, N.R., Group, M.S., 2007. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 114, 1868–1875.
- Kamba, T., McDonald, D.M., 2007. Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br. J. Canc.* 96, 1788–1795.
- Keenan, T.D., Kelly, S.P., Sallam, A., Mohamed, Q., Tufail, A., Johnston, R.L., 2013. Incidence and baseline clinical characteristics of treated neovascular age-related macular degeneration in a well-defined region of the UK. *Br. J. Ophthalmol.* 97, 1168–1172.
- Kim, L.N., Mehta, H., Barthelmes, D., Nguyen, V., Gillies, M.C., 2016. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* 36, 1418–1431.
- Kumar, A., Sahni, J.N., Stangos, A.N., Campa, C., Harding, S.P., 2011. Effectiveness of ranibizumab for neovascular age-related macular degeneration using clinician-determined retreatment strategy. *Br. J. Ophthalmol.* 95, 530–533.
- Lains, I., Duarte, D., Barros, A.S., Martins, A.S., Gil, J., Miller, J.B., Marques, M., Mesquita, T., Kim, I.K., Cachulo, M.D.L., Vavvas, D., Carreira, I.M., Murta, J.N., Silva, R., Miller, J.W., Husain, D., Gil, A.M., 2017. Human plasma metabolomics in age-related macular degeneration (AMD) using nuclear magnetic resonance spectroscopy. *PLoS One* 12, e0177749.
- Lalwani, G.A., Rosenfeld, P.J., Fung, A.E., Dubovy, S.R., Michels, S., Feuer, W., Davis, J.L., Flynn Jr., H.W., Esquiabro, M., 2009. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrOnto Study. *Am. J. Ophthalmol.* 148, e41 43–58.
- Lambert, N.G., ElShelmani, H., Singh, M.K., Mansergh, F.C., Wride, M.A., Padilla, M., Keegan, D., Hogg, R.E., Ambati, B.K., 2016. Risk factors and biomarkers of age-related macular degeneration. *Prog. Retin. Eye Res.* 54, 64–102.
- Lamoureaux, E.L., Pallant, J.F., Pesudovs, K., Rees, G., Hassell, J.B., Keeffe, J.E., 2007. The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and rasch analysis. *Invest. Ophthalmol. Vis. Sci.* 48, 1001–1006.
- Lee, A.Y., Lee, C.S., Butt, T., Xing, W., Johnston, R.L., Chakravarthy, U., Egan, C., Akerele, T., McKibbin, M., Downey, L., Natha, S., Bailey, C., Khan, R., Antcliff, R., Varma, A., Kumar, V., Tsaloumas, M., Mandal, K., Liew, G., Keane, P.A., Sim, D., Bunce, C., Tufail, A., Group, U.A.E.U., 2015. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. *Br. J. Ophthalmol.* 99, 1045–1050.
- Lee, A.Y., Day, A.C., Egan, C., Bailey, C., Johnston, R.L., Tsaloumas, M.D., Denniston, A.K., Tufail, A., United Kingdom Age-related Macular, D., Diabetic Retinopathy Electronic Medical Records Users, G., 2016. Previous intravitreal therapy is associated with increased risk of posterior capsule rupture during cataract surgery. *Ophthalmology* 123, 1252–1256.
- Lee, C.S., Baughman, B.S., Lee, A.Y., 2017. Deep learning is effective for classifying normal versus age-related macular degeneration OCT images. *Ophthalmol. Retina* 1 (4), 322–327.
- Lee, A.Y., Lee, C.S., Egan, C.A., Bailey, C., Johnston, R.L., Natha, S., Hamilton, R., Khan, R., Al-Husainy, S., Brand, C., Akerele, T., McKibbin, M., Downey, L., Tufail, A., Dec 2017a. UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice. *Br. J. Ophthalmol.* 101 (12), 1683–1688. <http://dx.doi.org/10.1136/bjophthalmol-2016-309818>. Epub 2017 May 6.
- Lee, C.S., Kim, A.J., Baughman, D., Egan, C., Bailey, C., Johnston, R.L., Natha, S., Khan, R., Brand, C., Akerele, T., McKibbin, M., Downey, L., Al-Husainy, S., Lee, A.Y., Tufail, A., 11 Apr 2017b. Visual acuity improvement when switching from ranibizumab to aflibercept is not sustained. *Retina*. <http://dx.doi.org/10.1097/IAE.0000000000001637>. [Epub ahead of print].
- Li, P., Stuart, E.A., Allison, D.B., 2015. Multiple imputation: a flexible tool for handling missing data. *JAMA* 314, 1966–1967.
- Liew, G., Lee, A.Y., Zarranz-Ventura, J., Stratton, I., Bunce, C., Chakravarthy, U., Lee, C.S., Keane, P.A., Sim, D.A., Akerele, T., McKibbin, M., Downey, L., Natha, S., Bailey, C., Khan, R., Antcliff, R., Armstrong, S., Varma, A., Kumar, V., Tsaloumas, M., Mandal, K., Egan, C., Johnston, R.L., Tufail, A., 2016. The UK Neovascular AMD Database Report 3: inter-centre variation in visual acuity outcomes and establishing real-world measures of care. *Eye (Lond)* 30, 1462–1468.
- Lotery, A., Griner, R., Ferreira, A., Milnes, F., Dugel, P., 2017. Real-world visual acuity outcomes between ranibizumab and aflibercept in treatment of neovascular AMD in a large US data set. *Eye (Lond)* 31, 1697–1706.
- Lum, F., Schachat, A.P., Jampel, H.D., 2002. The development and demise of a cataract surgery database. *Jt. Comm. J. Qual. Improv.* 28, 108–114.
- Madhusudhana, K.C., Lee, A.Y., Keane, P.A., Chakravarthy, U., Johnston, R.L., Egan, C.A., Sim, D., Zarranz-Ventura, J., Tufail, A., McKibbin, M., Group, U.A.E.S., 2016. UK Neovascular Age-Related Macular Degeneration Database. Report 6: time to retreatment after a pause in therapy. Outcomes from 92 976 intravitreal ranibizumab injections. *Br. J. Ophthalmol.* 100, 1617–1622.
- Marella, M., Pesudovs, K., Keeffe, J.E., O'Connor, P.M., Rees, G., Lamoureaux, E.L., 2010. The psychometric validity of the NEI VFQ-25 for use in a low-vision population. *Invest. Ophthalmol. Vis. Sci.* 51, 2878–2884.
- Martin, D.F., Maguire, M.G., Fine, S.L., Ying, G.S., Jaffe, G.J., Grunwald, J.E., Toth, C., Redford, M., Ferris, F.L., Group, C.o.a.-r.m.d.t.t.c.r., 2012. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 119, 1388–1398.
- McNamara, R.L., Spatz, E.S., Kelley, T.A., Stowell, C.J., Beltrame, J., Heidenreich, P., Tresserras, R., Jernberg, T., Chua, T., Morgan, L., Panigrahi, B., Rosas Ruiz, A., Rumsfeld, J.S., Sadwin, L., Schoeberl, M., Shahian, D., Weston, C., Yeh, R., Lewin, J., 2015. Standardized outcome measurement for patients with coronary artery disease: consensus from the international Consortium for health outcomes measurement (ICHOM). *J. Am. Heart Assoc.* 4.
- Menghini, M., Kloeckener-Gruissem, B., Fleischhauer, J., Kurz-Levin, M.M., Sutter, F.K., Berger, W., Barthelmes, D., 2012. Impact of loading phase, initial response and CFH genotype on the long-term outcome of treatment for neovascular age-related macular degeneration. *PLoS One* 7, e42014.
- Michaelson, I.C., 1948. The mode of development of the vascular system of the retina: with some observations on its significance for certain retinal diseases. *Trans. Ophthalmol. Soc. U. K.* 68, 137–180.
- Michels, S., Rosenfeld, P.J., Puliafito, C.A., Marcus, E.N., Venkatraman, A.S., 2005. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 112, 1035–1047.
- Miller, J.W., Adamis, A.P., Aiello, L.P., 1997. Vascular endothelial growth factor in ocular neovascularization and proliferative diabetic retinopathy. *Diabetes Metab. Rev.* 13, 37–50.
- Minassian, D.C., Reidy, A., Lightstone, A., Desai, P., 2011. Modelling the prevalence of age-related macular degeneration (2010–2020) in the UK: expected impact of anti-vascular endothelial growth factor (VEGF) therapy. *Br. J. Ophthalmol.* 95, 1433–1436.
- Molnar, F.J., Hutton, B., Fergusson, D., 2008. Does analysis using "last observation carried forward" introduce bias in dementia research? *CMAJ* 179, 751–753.
- Murphy, K.P., 2012. Machine Learning: A Probabilistic Perspective. Adaptive Computation and Machine Learning Series. MIT Press.
- Ng, W.Y., Tan, G.S., Ong, P.G., Cheng, C.Y., Cheung, C.Y., Wong, D.W., Mathur, R., Chow, K.Y., Wong, T.Y., Cheung, G.C., 2015. Incidence of myocardial infarction, stroke, and death in patients with age-related macular degeneration treated with intravitreal anti-vascular endothelial growth factor therapy. *Am. J. Ophthalmol.* 159, e551 557–564.
- NICE, 2008. Ranibizumab and Pegaptanib for the Treatment of Age-related Macular Degeneration.
- NICE, 2013. Aflibercept Solution for Injection for Treating Wet Age-related Macular Degeneration.
- Ozturk, M., Harris, Nguyen, V., Barthelmes, D., Gillies, M.C., Mehta, H., 2017 Oct 17. Real-world visual outcomes in patients with neovascular age-related macular degeneration receiving aflibercept at fixed intervals as per UK licence. *Clin. Exp. Ophthalmol.* <http://dx.doi.org/10.1111/ceo.13085>. [Epub ahead of print].
- Parangi, S., O'Reilly, M., Christofori, G., Holmgren, L., Grosfeld, J., Folkman, J., Hanahan, D., 1996. Antiangiogenic therapy of transgenic mice impairs de novo tumor growth.

- Proc. Natl. Acad. Sci. U.S.A 93, 2002–2007.
- Pecen, P.E., Kaiser, P.K., 2015. Current phase 1/2 research for neovascular age-related macular degeneration. *Curr. Opin. Ophthalmol.* 26, 188–193.
- Pushpooth, S., Sykakis, E., Merchant, K., Browning, A.C., Gupta, R., Talks, S.J., 2012. Measuring the benefit of 4 years of intravitreal ranibizumab treatment for neovascular age-related macular degeneration. *Br. J. Ophthalmol.* 96, 1469–1473.
- Razavi, H., Arnold, J., Guymer, R., 2015. To dry or not too dry: should we be more tolerant of stable subretinal fluid in patients receiving anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration? *Clin. Exp. Ophthalmol.* 43, 707–710.
- Regillo, C.D., Brown, D.M., Abraham, P., Yue, H., Ianchulev, T., Schneider, S., Shams, N., 2008. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am. J. Ophthalmol.* 145, 239–248.
- Rodrigues, I.A., Sprinkhuizen, S.M., Barthelme, D., Blumenkranz, M., Cheung, G., Haller, J., Johnston, R., Kim, R., Klaver, C., McKibbin, M., Ngah, N.F., Pershing, S., Shankar, D., Tamura, H., Tufail, A., Weng, C.Y., Westborg, I., Yelf, C., Yoshimura, N., Gillies, M.C., 2016. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. *Am. J. Ophthalmol.* 168, 1–12.
- Rofagha, S., Bhisitkul, R.B., Boyer, D.S., Sadda, S.R., Zhang, K., Group, S.-U.S., 2013. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology* 120, 2292–2299.
- Rosenfeld, P.J., Moshfeghi, A.A., Puliafito, C.A., 2005. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg. Laser. Imag.* 36, 331–335.
- Rosenfeld, P.J., Brown, D.M., Heier, J.S., Boyer, D.S., Kaiser, P.K., Chung, C.Y., Kim, R.Y., Group, M.S., 2006. Ranibizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* 355, 1419–1431.
- Ross, A.H., Donachie, P.H., Sallam, A., Stratton, I.M., Mohamed, Q., Scanlon, P.H., Kirkpatrick, J.N., Johnston, R.L., 2013. Which visual acuity measurements define high-quality care for patients with neovascular age-related macular degeneration treated with ranibizumab? *Eye (Lond)* 27, 56–64.
- Rudnicka, A.R., Jarrar, Z., Wormald, R., Cook, D.G., Fletcher, A., Owen, C.G., 2012. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology* 119, 571–580.
- Salathe, M., Khandelwal, S., 2011. Assessing vaccination sentiments with online social media: implications for infectious disease dynamics and control. *PLoS Comput. Biol.* 7, e1002199.
- Salathe, M., Bengtsson, L., Bodnar, T.J., Brewer, D.D., Brownstein, J.S., Buckee, C., Campbell, E.M., Cattuto, C., Khandelwal, S., Mabry, P.L., Vespignani, A., 2012. Digital epidemiology. *PLoS Comput. Biol.* 8, e1002616.
- Schmidt-Erfurth, U., Waldstein, S.M., 2016. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog. Retin. Eye Res.* 50, 1–24.
- Schmidt-Erfurth, U., Kaiser, P.K., Korobelnik, J.F., Brown, D.M., Chong, V., Nguyen, Q.D., Ho, A.C., Ogura, Y., Simader, C., Jaffe, G.J., Slakter, J.S., Yancopoulos, G.D., Stahl, N., Vitti, R., Berliner, A.J., Soo, Y., Anderesi, M., Sowade, O., Zeitz, O., Norenberg, C., Sandbrink, R., Heier, J.S., 2014. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 121, 193–201.
- Schmidt-Erfurth, U., Bogunovic, H., Sadeghipour, A., Schlegl, T., 2017. Machine learning to analyze the prognostic value of current imaging biomarkers in neovascular age-related macular degeneration. *Ophthalmol. Retina* 2 (1), 24–30.
- Senger, D.R., Galli, S.J., Dvorak, A.M., Perruzzi, C.A., Harvey, V.S., Dvorak, H.F., 1983. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 219, 983–985.
- Shalchi, Z., Okada, M., Whiting, C., Hamilton, R., 2017. Risk of posterior capsule rupture during cataract surgery in eyes with previous intravitreal injections. *Am. J. Ophthalmol.* 177, 77–80.
- Sherman, R.E., Anderson, S.A., Dal Pan, G.J., Gray, G.W., Gross, T., Hunter, N.L., LaVange, L., Marinac-Dabic, D., Marks, P.W., Robb, M.A., Shuren, J., Temple, R., Woodcock, J., Yue, L.Q., Califf, R.M., 2016. Real-world evidence - what is it and what can it tell us? *N. Engl. J. Med.* 375, 2293–2297.
- Silva, R., Axer-Siegel, R., Eldem, B., Guymer, R., Kirchhof, B., Papp, A., Seres, A., Gekkieva, M., Nieweg, A., Pilz, S., Group, S.S., 2013. The SECURE study: long-term safety of ranibizumab 0.5 mg in neovascular age-related macular degeneration. *Ophthalmology* 120, 130–139.
- Souied, E.H., Oubraham, H., Mimoun, G., Cohen, S.Y., Quere, S., Derveloy, A., Group, T.S., 2015. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the TWIN Study. *Retina* 35, 1743–1749.
- Spaide, R.F., Laud, K., Fine, H.F., Klancknik, J.M., Meyerle, C.B., Yannuzzi, L.A., Sorenson, J., Slakter, J., Fisher, Y.L., Cooney, M.J., 2006. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 26, 383–390.
- Sparrow, J.M., Taylor, H., Qureshi, K., Smith, R., Birnie, K., Johnston, R.L., group, U.E.u., 2012. The Cataract National Dataset electronic multi-centre audit of 55,567 operations: risk indicators for monocular visual acuity outcomes. *Eye (Lond)* 26, 821–826.
- Steinbrook, R., 2006. The price of sight—ranibizumab, bevacizumab, and the treatment of macular degeneration. *N. Engl. J. Med.* 355, 1409–1412.
- STROBE, 2007. STROBE Checklists 2007. Version 4 as published in Oct/Nov 2007. .
- Talks, J.S., Lotery, A.J., Ghanchi, F., Sivaprasad, S., Johnston, R.L., Patel, N., McKibbin, M., Bailey, C., Mahmood, S., United Kingdom Aflibercept Users, G., 2016. First-year visual acuity outcomes of providing aflibercept according to the VIEW study protocol for age-related macular degeneration. *Ophthalmology* 123, 337–343.
- Thijssen, V.L., Postel, R., Brandwijk, R.J., Dings, R.P., Nesmelova, I., Satijn, S., Verhofstad, N., Nakabeppu, Y., Baum, L.G., Bakkers, J., Mayo, K.H., Poirier, F., Griffioen, A.W., 2006. Galectin-1 is essential in tumor angiogenesis and is a target for antiangiogenesis therapy. *Proc. Natl. Acad. Sci. U.S.A* 103, 15975–15980.
- Tolentino, M.J., McLeod, D.S., Taomoto, M., Otsuji, T., Adamis, A.P., Luty, G.A., 2002. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. *Am. J. Ophthalmol.* 133, 373–385.
- Tufail, A., Patel, P.J., Egan, C., Hykin, P., da Cruz, L., Gregor, Z., Dowler, J., Majid, M.A., Bailey, C., Mohamed, Q., Johnston, R., Bunce, C., Xing, W., Investigators, A.B.C.T., 2010. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ* 340, c2459.
- Tufail, A., et al., 2014. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology* 121, 1092–1101.
- van Asten, F., Evers-Birkenkamp, K.U., van Lith-Verhoeven, J.J., de Jong-Hesse, Y., Hoppenreijts, V.P., Hommersom, R.F., Scholten, A.M., Hoyng, C.B., Klaver, J.H., group, H.s., 2015. A prospective, observational, open-label, multicentre study to investigate the daily treatment practice of ranibizumab in patients with neovascular age-related macular degeneration. *Acta Ophthalmol.* 93, 126–133.
- Vaze, A., Fraser-Bell, S., Gillies, M., 2014. Consequences of long-term discontinuation of vascular endothelial growth factor inhibitor therapy in the patients with neovascular age-related macular degeneration. *Acta Ophthalmol.* 92, e697–698.
- Verteporfin In Photodynamic Therapy Study, G., 2001. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization—verteporfin in photodynamic therapy report 2. *Am. J. Ophthalmol.* 131, 541–560.
- Virgili, G., Parravano, M., Menchini, F., Evans, J.R., 2014. Anti-vascular endothelial growth factor for diabetic macular oedema. *Cochrane Database Syst. Rev.*, CD007419.
- Watson, S., Daniell, M., Chan, E., Kerdraon, Y., Males, J., Morlet, N., Beckingsale, P., Mills, R., Go, C., Barthelme, D., 2017. The Outcomes of Corneal Cross-linking for Keratoconus Form Routine Clinical Practice across Australia and New Zealand: Results from the Save Sight Registries Keratoconus Module. Stephanie Watson, Mark Daniell, Elsie Chan, Yves Kerdraon, John Males, Nigel Morlet, Peter Beckingsale, Richard Mills, Chris Go, Daniel Barthelme, Martina Knecht-Bosch, Amparo Herrera-Bond, Vuong Nguyen, Amanda Dinh, Courtney Weston, Marco Garcia, Mark Gillies. ARVO Baltimore USA 2017. ARVO, Baltimore, USA.
- Westberg, I.A.S., Bjärnhall, G., Granstam, E., Johansson, I., Karlsson, N., 2014. The Swedish Macula Register - results, adverse events and safety in intravitreal injections. *Invest. Ophthalmol. Vis. Sci.* 55, 1.
- Westberg, I., Albrecht, S., Rosso, A., 2017 Nov. Risk for low visual acuity after 1 and 2 Years of treatment with ranibizumab or bevacizumab for patients with neovascular age-related macular degeneration. *Retina* 37 (11), 2035–2046. <http://dx.doi.org/10.1097/IAE.0000000000001431>.
- Willis, J., Morse, L., Vitale, S., Parke 2nd, D.W., Rich, W.L., Lum, F., Cantrell, R.A., 2017 Jul. Treatment patterns for myopic choroidal neovascularization in the United States: analysis of the IRIS registry. *Ophthalmology* 124 (7), 935–943. <http://dx.doi.org/10.1016/j.ophtha.2017.02.018>. Epub 2017 Mar 31.
- Wolf, A., Kampik, A., 2014. Efficacy of treatment with ranibizumab in patients with wet age-related macular degeneration in routine clinical care: data from the COMPASS health services research. *Graefes Arch. Clin. Exp. Ophthalmol.* 252, 647–655.
- Wong, W.L., Su, X., Li, X., Cheung, C.M., Klein, R., Cheng, C.Y., Wong, T.Y., 2014. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob. Health* 2, e106–116.
- Wong, C.W., Yanagi, Y., Lee, W.K., Ogura, Y., Yeo, I., Wong, T.Y., Cheung, C.M.G., 2016. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. *Prog. Retin. Eye Res.* 53, 107–139.
- Wood, A.M., White, I.R., Thompson, S.G., 2004. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clin. Trials* 1, 368–376.
- Wykoff, C.C., Ou, B., Brown, D., Croft, D., 2017. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration. *Retina* 1, 8.
- Yang, Y., Downey, L., Mehta, H., Mushtaq, B., Narendran, N., Patel, N., Patel, P.J., Ayan, F., Gibson, K., Igwe, F., Jeffery, P., 2017. Resource use and real-world outcomes for ranibizumab treat and extend for neovascular age-related macular degeneration in the UK: interim results from TERRA. *Ophthalmol. Ther.* 6, 175–186.
- Zarranz-Ventura, J., Liew, G., Johnston, R.L., Xing, W., Akerele, T., McKibbin, M., Downey, L., Natha, S., Chakravarthy, U., Bailey, C., Khan, R., Antcliff, R., Armstrong, S., Varma, A., Kumar, V., Tsaloumas, M., Mandal, K., Bunce, C., Tufail, A., United Kingdom Age-Related Macular Degeneration Electronic Medical Records Users, G., 2014. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology* 121, 1966–1975.