Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial

*Sobha Sivaprasad, A Toby Prevost, Joana C Vasconcelos, Amy Riddell, Caroline Murphy, Joanna Kelly, James Bainbridge, Rhiannon Tudor-Edwards, David Hopkins, Philip Hykin, on behalf of the CLARITY Study Group**

Summary

Background **Proliferative diabetic retinopathy is the most common cause of severe sight impairment in people with diabetes. Proliferative diabetic retinopathy has been managed by panretinal laser photocoagulation (PRP) for the past 40 years. We report the 1 year safety and efficacy of intravitreal aflibercept.**

Methods **In this phase 2b, single-blind, non-inferiority trial (CLARITY), adults (aged ≥18 years) with type 1 or 2 diabetes and previously untreated or post-laser treated active proliferative diabetic retinopathy were recruited from 22 UK ophthalmic centres. Patients were randomly assigned (1:1) to repeated intravitreal aflibercept (2 mg/0·05 mL at baseline, 4 weeks, and 8 weeks, and from week 12 patients were reviewed every 4 weeks and aflibercept injections were given as needed) or PRP standard care (single spot or mutlispot laser at baseline, fractionated fortnightly thereafter, and from week 12 patients were assessed every 8 weeks and treated with PRP as needed) for 52 weeks. Randomisation was by minimisation with a web-based computer generated system. Primary outcome assessors were masked optometrists. The treating ophthalmologists and participants were not masked. The primary outcome was defined as a change in best-corrected visual acuity at 52 weeks with a linear mixed-effect model that estimated adjusted treatment effects at both 12 weeks and 52 weeks, having excluded fluctuations in best corrected visual acuity owing to vitreous haemorrhage. This modified intention-to-treat analysis was reapplied to the per protocol participants. The non-inferiority margin was prespecified as –5 Early Treatment Diabetic Retinopathy Study letters. Safety was assessed in all participants. This trial is registered with ISRCTN registry, number 32207582.**

Findings **We recruited 232 participants (116 per group) between Aug 22, 2014 and Nov 30, 2015. 221 participants (112 in aflibercept group, 109 in PRP group) contributed to the modified intention-to-treat model, and 210 participants (104 in aflibercept group and 106 in PRP group) within per protocol. Aflibercept was non-inferior and superior to PRP in both the modified intention-to-treat population (mean best corrected visual acuity difference 3·9 letters [95% CI 2·3–5·6], p<0·0001) and the per-protocol population (4·0 letters [2·4–5·7], p<0·0001). There were no safety concerns. The 95% CI adjusted difference between groups was more than the prespecified acceptable margin of –5 letters at both 12 weeks and 52 weeks.**

Interpretation **Patients with proliferative diabetic retinopathy who were treated with intravitreal aflibercept had an improved outcome at 1 year compared with those treated with PRP standard care.**

Funding **The Efficacy and Mechanism Evaluation Programme, a Medical Research Council and National Institute for Health Research partnership.**

Lancet 2017; 389: 2193–203

Published **Online** May 7, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31193-5

See **Editorial** page 2163

See **Comment** page 2165

*Members are listed at the end of the paper

National Institute for Health Research, Moorfields Biomedical Research Centre, London, UK (Prof S Sivaprasad FRCOphth, P Hykin FRCOphth); **Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK** (Prof A Toby Prevost PhD, J C Vasconcelos MSc); **King's Clinical Trials Unit at King's Health Partners, King's College London, London, UK** (A Riddell PhD, C Murphy MS, J Kelly MSc); **University College London Institute of Ophthalmology, London, UK** (Prof J Bainbridge FRCOphth); **Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, Gwynedd, UK** (Prof R Tudor-Edwards DPhil); **and Department of Diabetes and Endocrinology, King's College Hospital NHS Foundation Trust, London, UK** (D Hopkins FRCP)

Correspondence to: Prof Sobha Sivaprasad, National Institute for Health Research, Moorfields Biomedical Research Centre, London, EC1V 2PD, UK **Sobha.sivaprasad@moorfields.nhs.uk**

Introduction

Proliferative diabetic retinopathy (PDR) is the commonest cause of severe visual loss in people with diabetes.[1] This condition is characterised by the growth of new abnormal vessels on the retina or optic disc that can result in sight threatening complications such as vitreous haemorrhage and tractional retinal detachment.

Panretinal laser photocoagulation (PRP) has been the standard of care for this condition for more than 40 years and reduces the risk of severe visual loss by 50%.[2] Patients identified with active PDR are treated urgently to complete initial PRP and then reviewed regularly to identify and treat recurrent or de novo active neovascularisation with supplemental PRP. Repeated supplemental PRP is associated with permanent sequelae on visual function including final visual acuity below the driving standard, restricted visual fields that preclude driving, night vision difficulties, loss of colour vision and reduced contrast sensitivity, and increased macular oedema.[3–7] Although laser technology and techniques have evolved over the past decade to reduce side-effects,[5,6] approximately 4·5% progress to require vitrectomy

Research in context

Evidence before this study

Panretinal laser photocoagulation (PRP) is the standard of care for patients with proliferative diabetic retinopathy. Presently, three anti-vascular endothelial growth factor (anti-VEGF) therapeutic agents are administered by intravitreal injections to treat ophthalmic conditions. Bevacizumab and ranibizumab are monoclonal antibodies against VEGF-A. Before this trial, we reviewed PubMed articles published between Jan 1, 2005, and Jan 31, 2014, and there were eight short-term (3–6 months), randomised controlled trials comparing either bevacizumab or ranibizumab monotherapy or in combination with PRP versus PRP alone in high-risk patients with proliferative diabetic retinopathy. These randomised controlled trials showed new vessel regression with these biological agents within 3–4 months. Aflibercept is the latest anti-VEGF agent and it blocks all isomers of VEGF-A, VEGF-B, placental growth factor 1, placental growth factor 2, and galectin-1. To date, there have been no randomised controlled trials of aflibercept in patients with proliferative diabetic retinopathy.

We updated the literature review on March 1, 2017. A well designed multicentre clinical trial comparing ranibizumab monotherapy versus PRP in patients with high-risk proliferative diabetic retinopathy, with and without macular oedema, has been published. The primary outcome of this randomised controlled trial at 2 years showed non-inferiority of ranibizumab versus PRP in patients at a high risk of proliferative diabetic retinopathy with a median of ten injections over 2 years (seven injections in the first year). However, this trial has not changed clinical practice worldwide due to the perceived practical difficulties of delivering repeated intravitreal injections in patients with proliferative diabetic retinopathy. Additionally, the study only showed non-inferiority of best corrected visual acuity to PRP, albeit with beneficial secondary outcomes. Therefore, PRP remains the preferred choice. Additionally, a substantial proportion of patients after initial PRP are under long-term follow-up in retinal clinics to identify and treat reactivation of existing neovascularisation with supplemental PRP and these patients have been excluded from previous clinical trials. Therefore, the role of anti-VEGF in this patient cohort remains unclear.

Added value of this study

The CLARITY study is the first randomised controlled trial, to our knowledge, of intravitreal aflibercept in proliferative diabetic retinopathy and the results provide substantial evidence that the visual outcome of active proliferative diabetic retinopathy at 1 year with aflibercept therapy is superior to PRP. This study is also the first to show a superior visual acuity outcome with an anti-VEGF agent in eyes with proliferative diabetic retinpathy with no baseline macular oedema compared with PRP therapy. Furthermore, this effect was achieved with four aflibercept injections (a median of one injection after the three loading doses in a year) irrespective of the proliferative diabetic retinopathy risk status and previous PRP treatment history, providing important evidence that aflibercept therapy can be adopted as an alternative to PRP in the first year of therapy. The study also showed a significantly lower incidence of macular oedema and vitreous haemorrhage and fewer adverse effects on binocular visual acuity and visual fields with aflibercept compared with PRP, further highlighting the advantages of aflibercept over PRP with similar systemic adverse effects. Most importantly, the patient satisfaction scores suggest a patient preference for aflibercept therapy over PRP in a clinical trial setting.

Implications of all the available evidence

In the first year of therapy, aflibercept is an effective treatment for active proliferative diabetic retinopathy and might be adopted as an alternative option to PRP.

surgery.[8] Therefore, there is a substantial unmet need for novel treatments that reduce the risk of severe visual loss in PDR that is non-inferior to PRP with fewer side-effects.

Ranibizumab and bevacizumab, monoclonal antibody inhibitors of vascular endothelial growth factor A (VEGF-A), have been shown to cause short-term new vessel regression, either as monotherapy or in combination with PRP.[9] Since this study commenced, a randomised clinical trial comparing ranibizumab and PRP reported 2 year outcomes in high-risk PDR with and without macular oedema and showed ranibizumab monotherapy is non-inferior to PRP, with less visual field loss and incident vitrectomy.[10] The latest anti-VEGF agent, aflibercept, is a recombinant fusion protein comprising the binding domains of VEGF-1 and VEGF-2 receptors, binds to VEGF with a greater affinity than ranibizumab or bevacizumab, and shows activity against VEGF-A, VEGF-B, and placental growth factor.[11] This study is the first, to our knowledge, to assess efficacy and safety of intravitreal aflibercept in the management of PDR.

Methods

Study design and participants

CLARITY is a multicentre, prospective, two-arm, parallel-group, single-blind, randomised, controlled, phase 2b, non-inferiority trial. Patients were recruited from 22 UK National Health Service hospitals.

The study was granted approval by the National Research Ethics Committee Service London, South East (14/LO/0203). Clinical Trials Authorisation was given by the Medicines and Healthcare Products Regulatory Agency (11518/0013/001–0001) and the European Union Drug Regulating Authorities Clinical Trials (2013–003272–12). Trial steering and data monitoring committees provided independent oversight.

Eligible patients with type 1 or 2 diabetes, aged 18 years or older, with clinical evidence of previously untreated proliferative diabetic retinopathy or persistent retinal neovascularisation after initial PRP requiring additional PRP (ie, previously treated) were included. Best corrected visual acuity was 54 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters, equivalent to 6/24 Snellen best corrected visual acuity with sufficient media clarity and pupillary dilatation for adequate fundus photographs. The fellow eye Snellen best corrected visual acuity was 2/60 or higher. Women used effective contraception, or were post-menopausal for 12 months or more before trial entry, or surgically sterile. Study eye exclusion criteria were coexistent ocular disease that affected or might affect visual acuity or prevent treatment delivery. As diabetic macular oedema can coexist with PDR and confound visual acuity outcomes, all eyes with clinical evidence of diabetic macular oedema and spectral domain optical coherence tomography showing central subfield thickness of 300 µm or more due to macular oedema were excluded. Other ocular exclusions were moderate or dense vitreous haemorrhage preventing clear visualisation of the macula or optic disc or preventing laser treatment, fibrovascular proliferation, or tractional retinal detachment in the posterior pole, previous history of vitrectomy, other causes of retinal neovascularisation, and anticipated need for cataract extraction or vitrectomy within 12 months. Patients treated with intravitreal anti-VEGF or steroid for diabetic macular oedema within 4 months or PRP within 8 weeks before screening were excluded. Systemic exclusion criteria included glycated haemoglobin (HbA_{1c}) of 12% or higher, blood pressure of 170/110 mm Hg or higher, and any medical condition that, in the opinion of the investigator, precluded participation in the study. The clinical assessments schedule is detailed in the appendix and in the published protocol.[12]

Randomisation and masking

Patients provided informed consent and those eligible were randomly allocated (1:1) to either repeated intravitreal aflibercept 2 mg/0·05 mL (Bayer Pharma AG; Berlin, Germany) or PRP (single spot or multispot laser delivered as per standard of care) with the method of minimisation, concealed before allocation, stratified by site, baseline PDR status (previously untreated *vs* previously treated), best corrected visual acuity (54–69 *vs* ≥70 ETDRS letters), HbA_{1c} (<8% [<63·9 mmol/L], 8% to 10% [63·9–85·8 mmol/mol] and >10% [>85·8 mmol/mol]), diastolic blood pressure (≤90 mm Hg *vs* >90 mm Hg) by collaborating site investigators via the King's Clinical Trials Unit web-based randomisation service. Patients and clinical investigators were unmasked due to the anatomical changes induced by the comparator. Outcome assessors including optometrists, visual field technicians, imaging technicians, and the staff at the independent reading centre (The UK Network of Reading Centres, Belfast, UK) were masked to treatment allocation. The primary outcome assessors completed a treatment guess form to establish masking success.

Procedures

The intervention group received intravitreal aflibercept injections. The dose of each intravitreal aflibercept injection was 2 mg/0·05 mL and patients received mandated injections at baseline, 4 weeks, and 8 weeks. From week 12, patients were reviewed every 4 weeks and aflibercept injections were given as needed on the basis of the extent of regression and reactivation of neovascularisation of the optic disc and of clinical examination with adequate visualisation of the entire retina, and a comparison of seven-field colour photographs or wide-field photography at screening or previous visit. Patients were categorised into three groups according to treatment response: no regression, partial regression, and total regression to decide on retreatment based on predefined criteria (appendix). Treatment was deferred at the investigator's discretion when the eyes had adverse events such as vitreous haemorrhage, retinal detachment, or raised intraocular pressure of more than 30 mm Hg. If aflibercept became contraindicated during the trial (eg, newly pregnant woman), patients were treated with PRP. The comparator group received standard PRP treatment delivered as per routine clinical practice by direct or indirect, or single or multispot means targeting areas of non-perfusion initially. Patients in the PRP group had PRP at baseline and in fractionated fortnightly sessions thereafter, with follow-up at week 12. From week 12, patients in the PRP group were assessed for treatment response every 8 weeks and regression patterns categorised exactly as in the aflibercept group. Treatment in the PRP group was deferred if the media was too hazy or if the investigator judged that the eye had received adequate PRP.

See Online for appendix

Best corrected visual acuity was measured at 4 m by validated ETDRS visual acuity charts employing standard operating procedures for studies in diabetic retinopathy. Refracted visual acuity was done at screening, 12 weeks, 52 weeks, and withdrawal. Secondary outcomes included Pelli Robson contrast sensitivity letter scores, uniocular and binocular Esterman visual field efficiency score (missed spots), colour fundus photography, optical coherence tomography, and fundus fluorescein angiography. Patient-related outcomes were measured with validated questionnaires at screening and 52 weeks. These included National Eye Institute Vision Functioning Questionnaire 25, a diabetic retinopathy specific quality-of-life questionnaire, and diabetic retinopathy treatment satisfaction questionnaire. Health-related quality of life, activity scales, and health and social care service use will be reported in a subsequent cost-effectiveness paper. A subset of patients (n=40) also underwent oximetry and this mechanistic component of the study will be reported later.

Outcomes

The primary outcome was best corrected visual acuity letter change from baseline to 52 weeks in the study eye in the aflibercept group relative to the PRP group. A secondary outcome was best corrected visual acuity change from baseline to 12 weeks. Additional secondary visual function outcomes assessed at 52 weeks included uniocular and binocular Esterman missed spots, binocular visual acuity letter scores, low luminance visual acuity letter scores, categories of visual acuity outcomes in terms of visual gain or loss, and contrast sensitivity letter scores. Change from baseline between treatment groups in patient-reported outcomes with National Eye Institute Vision Functioning Questionnaire 25, diabetic retinopathy specific quality-of-life questionnaire, and diabetic retinopathy treatment satisfaction questionnaire at 52 weeks. Anatomical outcomes included new vessel regression patterns and change in ETDRS diabetic retinopathy severity score levels at 12 weeks and 52 weeks (appendix) measured by the UK Network of Reading Centres.[13] An improvement in diabetic retinopathy severity score is difficult to assess in lasered eyes and so the improvement of the level of remaining retinopathy was graded. The number of treatments required in both groups and the proportion of patients requiring supplemental PRP in the aflibercept group were reported. We assessed differences in ocular and systemic safety profiles between groups from baseline to 52 weeks. The vascular events as defined by the Antiplatelet Trialists' Collaboration were also compared between groups.[14]

Adverse events were recorded per visit, site investigators identified relatedness and the chief investigator (SS) identified expectedness of all serious adverse events. Adverse events were coded by two masked clinicians.

Statistical analysis

The intention-to-treat population was defined to comprise all randomly assigned patients. The per-protocol population was defined to exclude those randomly assigned patients who were ineligible at entry, and those not receiving the full allocated treatment up to and including the 8 week visit (whether due to discontinuation, exclusion, or another reason for missing a randomised treatment in this period). A statistical analysis plan was finalised before data lock and agreed with oversight committees. The primary outcome of refracted best corrected visual acuity was compared between groups primarily at 52 weeks and secondarily at 12 weeks with a linear mixed-effect model with patient as a random effect to allow for within-patient correlation of repeated measures over time. Fixed effects included the main effects and interactions with time (12 weeks and 52 weeks) for treatment group, the minimisation stratifiers: PDR status, contrasts for HbA_{1c}, blood pressure, the baseline of the outcome, and its missing indicator required for the missing indicator method.[15] As prespecified, any best corrected visual acuity measurement at 12 weeks and 52 weeks that was both more than 3 SD below the mean at that timepoint (including all measurements) and recorded within 3 months of the occurrence of a vitreous haemorrhage was excluded from analysis to avoid erroneous influence on the statistical analysis. Some sites recruited a very small number of patients and so the study site was not included in models to allow these patients to contribute to the estimation of treatment effects rather than site effects. The test for non-inferiority was one-sided at the 2·5% significance level, and is presented as an estimated effect with two-sided 95% CI compared with the non-inferiority margin of –5 letters. For the analysis of the primary outcome, the mixed effect model was refitted within the per protocol population. Analyses were completed according to the intention-to-treat strategy with intention-to-treat and per-protocol analyses modified for missing and excluded data together with principled sensitivity analysis in the full intention-to-treat and per protocol populations.[16,17] Secondary continuous outcomes were analysed only on the intention-to-treat basis modified for omitted data and with the same model specification as for the primary outcome, and reported as adjusted differences in means. All tests were two-sided at the 5% significance level and effect sizes had 95% CIs. Safety and other categorical outcomes are reported as proportions with 95% CIs and Pearson's χ^2 tests, or Fisher's exact tests and Wilson's exact CIs when any expected table counts were smaller than five.

A sensitivity assessment to the missing at random assumption made in the primary outcome analysis was undertaken in all patients who were randomly assigned for the handling of missing and excluded 52 week data, with three recommended scenarios affecting either one or both groups.[17] Sensitivity analysis was used to assess the use of concomitant treatments, to assess changes to conclusions from inclusion of isolated outliers in statistical analyses, defined as exceeding 4 SD from expected, and to assess additional adjustment for all sites as a fixed effect. If non-inferiority was concluded for the primary outcome, superiority could be assessed without the need to correct for multiple testing.

Preplanned subgroups were analysed for the primary outcomes by extension of the models to include interaction terms with the group for the randomisation stratifiers including baseline visual acuity, HbA_{1c}, diastolic blood pressure, and PDR status.

The planned sample size was 220 participants. Detailed sample size calculations are available in the published protocol.[12] The SD of the change in visual acuity, after adjustment for baseline, was anticipated to be 10·3, based on the estimate from a relevant trial.[18] In brief, the study had at least 90% power to detect non-inferiority of –5 letters using a two-sided 95% CI from an analysis of covariance test with adjustment for baseline visual acuity.[12,17]

This trial is registered with ISRCTN registry, number 32207582.

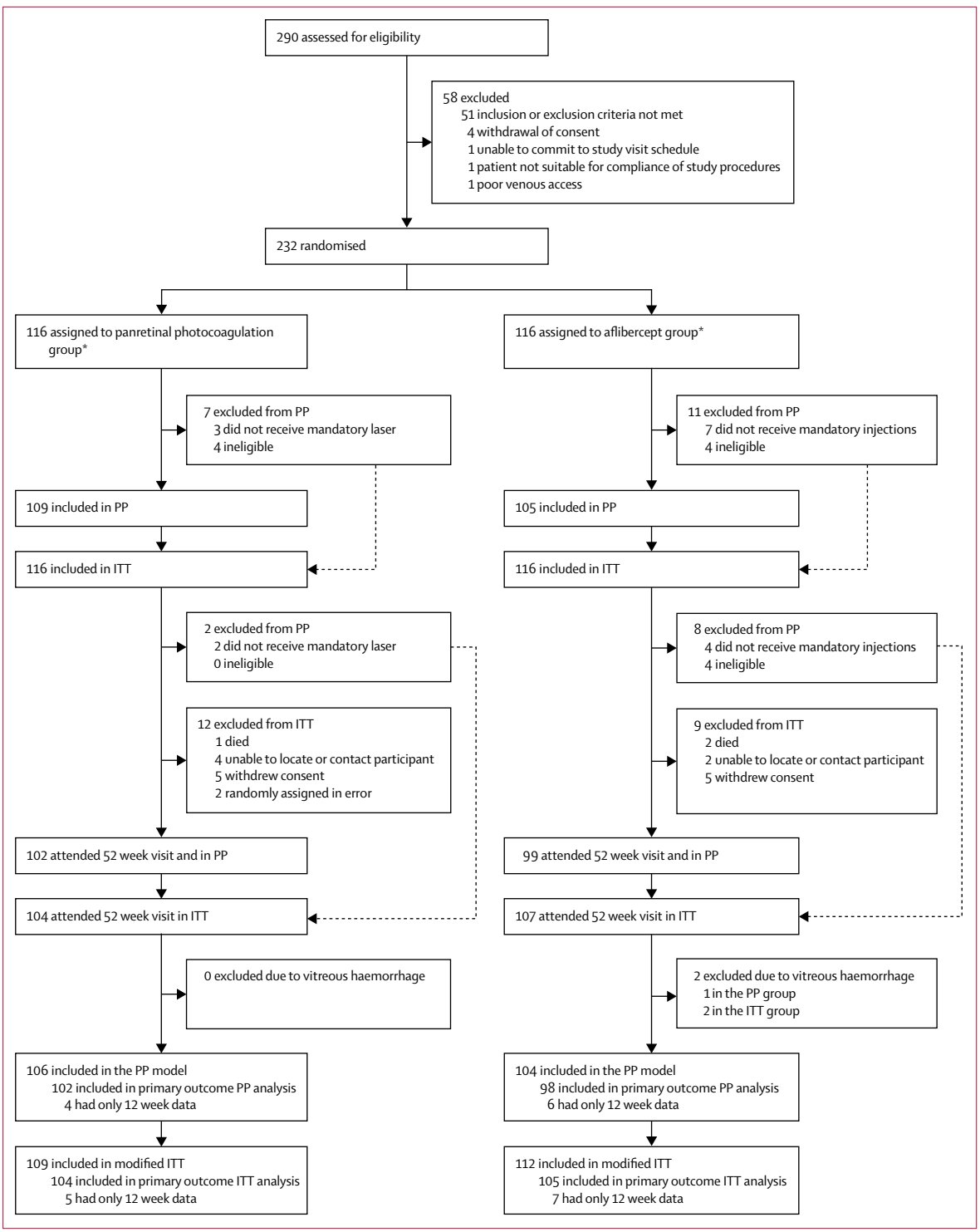

***Figure 1*: Trial profile**
ITT=Intention-to-treat population. PP=per-protocol population. *ITT population included in the sensitivity analysis.

Role of the funding source

Neither the funders nor the provider of active medication had any role in study design, patient recruitment, data collection, data analysis, data interpretation, writing, or editing the report or the decision to submit for publication. The statisticians had full access to all data in CLARITY and the chief investigator (SS) had final responsibility for the decision to submit for publication.

	PRP (%; n=116)	Aflibercept (%; n=116)
Age	50·8 (13·2)	51·5 (14·6)
Women	44 (38%)	33 (28%)
Men	72 (62%)	83 (72%)
Diabetes		
Type 1	51 (44%)	54 (47%)
Type 2	65 (56%)	62 (53%)
Medication		
Insulin only	53 (46%)	61 (53%)
Oral hypoglycaemic agents only	24 (21%)	26 (22%)
Insulin and oral hypoglycaemic agents	39 (34%)	29 (25%)
Diet controlled	0 (0%)	0 (0%)
Best corrected visual acuity (ETDRS letters)		
54–69	11 (9%)	10 (9%)
≥70	105 (91%)	106 (91%)
Lens status (study eye)		
Clear lens	80 (69%)	68 (59%)
Visually insignificant cataract	26 (22%)	37 (32%)
Visually significant cataract	0 (0%)	0 (0%)
Pseudophakia	10 (9%)	10 (9%)
Macular oedema (study eye)		
No macular oedema	87 (75%)	87 (76%)
Non-central macular oedema	28 (24%)	27 (23%)
Central macular oedema	1 (1%)	1 (1%)
Central subfield thickness (µm)	271·6 (28·1)	275·3 (30·9)*
Total volume (mm³)	8·94 (0·88)	8·99 (1·09)*
Proliferative diabetic retinopathy		
Treatment naive	63 (54%)	60 (52%)
Previously treated active PDR	53 (46%)	56 (48%)
Previous anti-VEGF therapy	5 (4%)	6 (5%)
Previous intravitreal steroid therapy	0 (0%)	1 (1%)
HbA_{1c}		
<8% (<63·90 mmol/mol)	44 (38%)	41 (35%)
8–10% (63·9–85·8 mmol/mol)	48 (41%)	51 (44%)
>10% (>85·81 mmol/mol)	24 (21%)	24 (21%)
Blood pressure (diastolic)		
≤90 mm Hg	102 (88%)	101 (87%)
>90 mm Hg	14 (12%)	15 (13%)

Data are mean (SD), n (%). ETDRS=Early Treatment Diabetic Retinopathy Study. PDR=proliferative diabetic retinopathy. *The optical coherence tomography medical imaging was not done for one participant (withdrew at baseline).

***Table 1*: Baseline characteristics in each treatment group**

Results

Between Aug 22, 2014 and Nov 30, 2015, 290 patients were assessed for eligibility and 232 were randomly assigned to receive intravitreal aflibercept (n=116) or PRP (n=116; figure 1).

Baseline characteristics were well balanced between treatment groups (table 1). Of 232 patients, a total of 123 (53%) previously untreated patients and 109 (47%) previously treated patients were recruited. Mean best corrected visual acuity at baseline was 81·4 ETDRS letters (SD 8·1). At baseline of 232 patients, 21 (9%) had best corrected visual acuity of 54–69 ETDRS letters and 211 (91%) had 70 or more ETDRS letters.

In the prespecified intention-to-treat population, the linear mixed-effect model of the best corrected visual acuity data were available for 211 (91%) of 232 patients (107 in the aflibercept group and 104 in the PRP group) at 52 weeks and for 214 (92%) of 232 patients at 12 weeks (n=109 and n=105). A total of four patients in the PRP group at 12 weeks and two patients in the aflibercept group at 52 weeks were excluded due to presence of vitreous haemorrhage within 3 months of best corrected visual acuity recordings and best corrected visual acuity was more than 3 SD below the mean at that timepoint (including all measurements). There were 198 patients with best corrected visual acuity data available at both 12 weeks and 52 weeks. A total of 11 patients had best corrected visual acuity recorded at 52 weeks and not 12 weeks (eight in the PRP group and three in the aflibercept group). Additionally, there were 12 patients who had best corrected visual acuity recorded at 12 weeks but not at 52 weeks (five in the PRP group and seven in the aflibercept group). Therefore, there were 221 patients that contributed to the analysis in the linear mixed effect model for the modified intention-to-treat analysis (109 in the PRP group and 112 in the aflibercept group).

A total of 18 patients did not meet the per-protocol definition and were not included in the per-protocol population (n=214; figure 1). This included 11 (10%) of 116 patients in the aflibercept group and seven (6%) of 116 patients in the PRP group, with four (3%) patients in the aflibercept group and four (3%) patients in the PRP group who were not compliant with the eligibility criteria. A further seven (6%) patients in the aflibercept group and three (3%) patients in the PRP group did not receive initial mandatory treatment requirements (figure 1). There were 191 patients with best corrected visual acuity data available at both 12 weeks and 52 weeks in the per-protocol analysis (95 in the PRP group and 96 in the aflibercept group). There were ten patients (four in the PRP group and six in the aflibercept group) that had data available only at 12 weeks but not at 52 weeks and a further nine patients (seven in the PRP group and two in the aflibercept group) with data only at 52 weeks (not at 12 weeks). Therefore, there were 210 patients that contributed to the per-protocol analysis in the linear mixed-effects model (106 in the PRP group and 104 in the aflibercept group).

The primary outcome at 52 weeks showed aflibercept was non-inferior and superior to PRP for best corrected visual acuity in both modified intention-to-treat population (mean best corrected visual acuity difference 3·9 letters [95% CI 2·3–5·6], p<0·0001) and the per-protocol population (difference 4·0 letters [2·4–5·7], p<0·0001; table 2). The adjusted difference between groups was more than the prespecified acceptable margin of –5 letters for the 95% CI at both 12 weeks and 52 weeks.

	n		Mean (SD)		Change from baseline Mean (SE)		Adjusted difference between groups (95% CI)	p value
	PRP	Aflibercept	PRP	Aflibercept	PRP	Aflibercept		
Baseline	116	116	81·9 (8·0)	80·9 (8·3)	..	..	..	..
At 12 weeks								
Intention to treat	101	109	81·3 (7·8)	82·6 (9·6)	−0·8 (0·4)	1·4 (0·5)	2·1 (0·5–3·7)*	0·0100
Per protocol	99	102	81·3 (7·9)	82·7 (9·7)	−0·9 (0·4)	1·5 (0·6)	2·3 (0·6–3·9)†	0·0074
At 52 weeks								
Intention to treat	104	105	79·1 (9·7)	82·4 (10·1)	−3·0 (0·7)	1·1 (0·6)	3·9 (2·3–5·6)*	<0·0001
Per protocol	102	98	79·3 (9·3)	82·6 (10·1)	−2·9 (0·7)	1·3 (0·6)	4·0 (2·4–5·7)†	<0·0001

PRP=panretinal photocoagulation. *The linear mixed-effects model incorporates 221 participants (n=109 PRP and n=112 aflibercept) with best corrected visual acuity at either 12 weeks or 52 weeks. †The linear mixed-effects model incorporates 210 participants (n=106 PRP and n=104 aflibercept) who have best corrected visual acuity at either 12 weeks or 52 weeks.

***Table 2*: Comparison of the primary outcome, best corrected visual acuity, between treatment groups at 12 weeks and 52 weeks**

Three sensitivity analyses on the population with completed follow-up at 52 weeks were done, adjusting for sites, excluding outliers, and assessing missing data assumptions. No patients were offered anti-VEGF treatment for macular oedema in the PRP group so sensitivity analysis for concomitant treatments was not required. When sites were considered, the adjusted difference in best corrected visual acuity between groups remained significant at 4·1 letters (95% CI 2·4–5·7), p<0·0001 in the modified intention-to-treat population and 4·1 letters (2·4–5·7, p<0·0001), in the per-protocol population. A total of 207 and 198 patients remained after outliers in the modified intention-to-treat and per-protocol populations, defined as less than or more than 4 SD, were removed. This sensitivity analysis showed the adjusted difference in best corrected visual acuity between groups as significant at 4·0 letters (95% CI 2·7–5·4, p<0·0001) in the modified intention-to-treat population and 4·1 letters (2·7–5·5, p<0·0001) in the per-protocol population. The sensitivity analysis for missing data also confirmed a superiority effect in both intention-to-treat (n=232) and per-protocol populations (n=214) for three prespecified alternative scenarios (figure 2, appendix). Primary outcomes in previously untreated and previously treated groups are shown in the appendix. The visual acuity in each stratum of visual acuity ranges at 52 weeks is also shown in the appendix.

Five (5%) of 101 patients had a greater or equal to ten letter improvement and was able to do so with baseline best corrected visual acuity of 90 or below in the aflibercept group compared with two (2%) of 95 patients in the PRP group (difference 2·8% [95% CI −3·1 to 9·1], p=0·45). Five (5%) of 107 patients had greater or equal to ten letter worsening in the aflibercept group compared with 16 (15%) of 104 in the PRP group (difference 10·7% [95% CI 2·6–19·3], p=0·009). Five (5%) of 107 patients had greater or equal to 15 letter worsening in the aflibercept group and six (6%) of 104 patients in the panretinal laser photocoagulation group (difference 1·1% [95% CI −5·5 to 7·9], p=0·72).

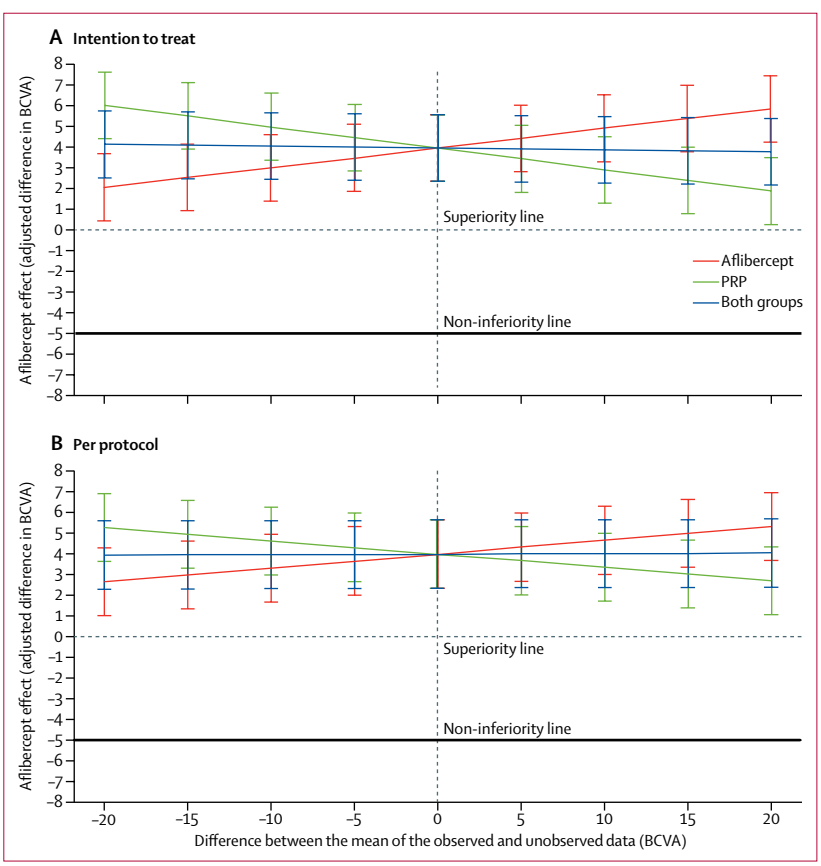

***Figure 2*: Sensitivity analysis with the missing at random assumption made in primary outcome analysis**
The main analysis assumed that those with missing data make no difference to the results. The sensitivity analysis assessed the impact on the treatment effect of aflibercept relative to PRP considering that the mean outcomes in those with unobserved data could range from minus 20 to plus 20 best corrected visual acuity letters from patients with observed data (horizontal axis). The treatment effect in the main analysis is shown at zero. Vertical bars are 95% CIs for the treatment effect displayed at five-letter intervals in the range. BCVA=best corrected visual acuity. PRP=panretinal photocoagulation.

Binocular Esterman scores showed significant worsening with the PRP group (appendix). This finding was also reflected in binocular visual acuity scores in the PRP group (appendix). Other visual function tests did not vary between groups. The appendix shows changes

	PRP (n=116)	Aflibercept (n=116)	p value
Endophthalmitis	0 (0%)	0 (0%)	..
Inflammation*	3 (3%)	9 (8%)	0·075
Visual disturbances	11 (9%)	10 (9%)	0·82
Ocular discomfort†	4 (3%)	6 (5%)	0·52
Cornea related problems‡	0 (0%)	5 (4%)	0·060
Retinal tear	0 (0%)	1 (1%)	1·00
Progression of cataract	1 (1%)	0 (0%)	1·00
Elevation in intraocular pressure	0 (0%)	1 (1%)	1·00
Iris neovascularisation	0 (0%)	0 (0%)	..
Neovascular glaucoma	0 (0%)	0 (0%)	..
Vitreoretinal interface abnormalities	1 (1%)	2 (2%)	1·00
Subconjunctival haemorrhage	0 (0%)	1 (1%)	1·00
Increasing severity of diabetic retinopathy	0 (0%)	1 (1%)	1·00
Macular oedema	2 (2%)	0 (0%)	0·50
Retinal detachment	0 (0%)	0 (0%)	..
New or increasing vitreous haemorrhage	21 (18%)	10 (9%)	0·034
Vitreous haemorrhage requiring vitrectomy	7 (6%)	1 (1%)	0·066

Data are n (%). PRP=panretinal photocoagulation. *Inflammation included reported conjunctivitis, uveitis, hordeolum, keratitis, blepharitis, and dacryoadenitis. Visual disturbance included floaters, flashing lights, nyctalopia, tunnel vision, decreased vision, nystagmus, and diplopia. †Ocular discomfort included pain, twitching, and foreign body sensation. ‡Corneal-related adverse events included corneal abrasion, punctate epithelial erosion, and conjunctival laceration. Vitreoretinal interface abnormalities included epiretinal membrane, posterior vitreous detachment, and lamellar hole.

***Table 3*: Ocular adverse events in study eye by treatment group at week 52**

	Panretinal laser photocoagulation (n=116)	Aflibercept (n=116)	p value
Non-fatal myocardial infarction	3 (3%)	3 (3%)	1·00
Non-fatal stroke	0 (0%)	3 (3%)	0·25
Vascular death	1 (1%)	2 (2%)	1·00
Unknown death	0 (0%)	0 (0%)	..
Any APTC event	4 (3%)	8 (7%)	0·24

Data are n (%). Events occurred at least once over 52 weeks. APTC=Anti-Platelet Trialists' Collaboration.

***Table 4*: APTC-defined events by treatment group**

in visual function in previously untreated and previously treated cohorts.

The diabetic retinopathy specific quality-of-life questionnaire scores and National Eye Institute Vision Functioning Questionnaire 25 scores did not show significant differences between groups (appendix). Diabetic retinopathy treatment satisfaction questionnaire scores showed that patient satisfaction scores were significantly better in the aflibercept group than in the PRP group and the adjusted mean difference was 3·0 (95% CI 0·4–5·5, p=0·022; appendix).

Macular thickness and volume significantly increased in the PRP group compared with the aflibercept group (appendix). The proportion of patients with no macular oedema at 52 weeks was 93 (89%) of 105 patients in the aflibercept group compared with 74 (71%) of 104 patients in the PRP group (appendix).

A significant proportion of eyes showed total regression of retinal new vessels in the aflibercept group compared with the PRP group (appendix). Total regression at 52 weeks favoured the aflibercept group with a difference between groups of 30% (95% CI 16–42, p<0·0001).

Of the 227 patients with gradable photographs, 175 (77%) patients had low-risk PDR (levels 61 and 65) and 52 (23%) patients had high-risk PDR (levels 71 and 75). Three eyes were graded below level 61 (appendix). Change in diabetic retinopathy severity level in previously untreated eyes with aflibercept is also reported in the appendix. A significantly higher proportion of patients in the PRP group (92 [90%]) remained at PDR (level 61 or above) compared with the aflibercept group (81 [78%]) at both 12 weeks and 52 weeks (p=0·016; appendix).

109 (94%) of 116 patients in the aflibercept group and 113 (97%) of 116 in the PRP group received treatment according to protocol. The treatment allocation guess form was reported for 210 participants. Of these, assessors guessed correctly for 32 (15%) patients, incorrectly for 20 (10%) patients, and were unable to tell for 158 (75%) patients.

By 52 weeks, patients treated with aflibercept received a mean of 4·4 (SD 1·7) injections (95% CI 4·1–4·7), and a median of 4·0 (IQR 3·0–5·0) including the three mandated loading doses. The mean number of aflibercept injections in previously untreated patients was 4·6 (SD 1·6) and a median of 4·0 (IQR 3·0–6·0), whereas previously treated patients received a mean number of 4·1 injections (1·8) and a median of 4·0 (3·0–4·8). Two (2%) of 116 patients required supplemental PRP in the aflibercept group.

In the PRP group, 78 (69%) of 113 patients received multispot laser and the remaining received single spot laser. The type of laser delivery was not recorded for three patients. Of 114 patients receiving PRP treatment, the distribution of PRP session numbers required from baseline were one session in 28 eyes (23%), two sessions in 26 eyes (22%), three sessions in 28 eyes (24%), four sessions in 19 eyes (17%), five sessions in ten eyes (9%), six sessions in two eyes (2%), and seven sessions in one eye (1%). From week 12, 75 (65%) of 116 patients in the PRP group required supplemental PRP. The mean number of supplemental PRP sessions required was 1·17 (SD 1·16; 95% CI 0·96–1·39) with previously untreated patients requiring 1·35 (1·28; 1·03–1·67) treatment sessions, and in the previously treated group the mean was 0·96 (0·96; 0·70–1·23).

With a comparison of other complications of PDR between groups, incidence of vitreous haemorrhage was higher in the PRP group (p=0·034). The proportion of patients requiring vitrectomy was small and not significant between groups (p=0·066; table 3). There were no cases of endophthalmitis in the study eye (table 3).

Ocular adverse events in the non-study eye are shown in the appendix. The number of vitreous haemorrhages in the non-study eye was recorded because this complication might confound both the vision-related and health-related quality-of-life assessments (appendix).

The Anti-Platelet Trialists' Collaboration defined events showed no significant differences between groups (table 4). Frequency of systemic adverse events did not differ between treatment group (appendix).

Discussion

The results of this phase 2b trial show that intravitreal aflibercept monotherapy is non-inferior and superior to standard PRP treatment for PDR through 52 weeks. This study is the first, to our knowledge, to show that an anti-VEGF therapy can provide superior best corrected visual acuity outcomes in eyes with active PDR without baseline centre-involving macular oedema. Mean differences in best corrected visual acuity letter score between groups in favour of aflibercept was small but significant, and was achieved with a median of one aflibercept injection only in the 40 weeks' post-loading phase, indicating that aflibercept is a feasible new approach for compliant patients.

Superior treatment satisfaction scores in the aflibercept group were unexpected but highlighted patients' preference for this therapy. The lower incidence of centre-involving macular oedema and vitreous haemorrhage reported in the aflibercept group might have contributed to both the mean best corrected visual acuity improvement and patient preference as these conditions are the most common causes of symptomatic visual impairment in patients with PDR. The proportion of patients with new onset centre-involving macular oedema also increased significantly in the PRP group. The incidence of vitreous haemorrhage was twice as high in the PRP group: 21 (18%) of 116 patients compared with ten (9%) of 116 patients in the aflibercept group.

Other factors that might explain the superior effect of aflibercept include a high aflibercept VEGF binding affinity and blockade of other angiogenic pathways such as placental growth factor and galectin-1.[19,20] However, the exact mechanisms of these pathways in PDR remain to be understood.

The superior best corrected visual acuity findings were supported by significantly better binocular visual acuity and binocular Esterman scores in the aflibercept group. These results have a significant effect on eligibility to retain a driving licence. In the UK, the Driver and Vehicle Licensing Agency have designated both a minimum visual acuity and Esterman visual field standard to maintain a valid driving licence.[21] With advances in laser technology and techniques, there are reports with a short follow-up suggesting that modern-day laser techniques and technology such as multispot laser have reduced the prevalence of visual field loss with PRP.[6,22,23] However, our study shows that despite 69% of the study cohort being treated with multispot laser, aflibercept is associated with lower risk of visual field loss than with a modern day laser at 52 weeks, in keeping with findings noted in the ranibizumab trial[10] in PDR at 2 years.

Other visual outcomes that measured adverse effects of PRP such as contrast sensitivity and low luminance visual acuity were not different between groups, although removing outliers suggested a greater preservation of low luminance visual acuity letter score by 52 weeks in the aflibercept group than in the PRP group.

Despite the good visual outcomes reported with this intervention with a median of only four injections in the first year, acceptance among in clinicians might vary because PRP is perceived to have a permanent effect and requires fewer follow-up visits than does anti-VEGF therapy. However, our study shows that 65% of the patients in the PRP group required supplemental PRP when monitored every 8 weeks over 52 weeks. The ranibizumab study also reported that 45% of the patients in the PRP group required additional sessions by the end of 2 years.[10] More importantly, loss of visual acuity of ten or more letters was three times more common with PRP than with aflibercept.

The disease-modifying effect of aflibercept is well established from diabetic macular oedema trials, in which aflibercept improves the level of diabetic retinopathy severity, alongside its effect on diabetic macular oedema.[24] This anatomical effect should also be considered when choosing between anti-VEGF and PRP as a first-line option in PDR. As aflibercept is licensed for diabetic macular oedema, the findings of this study indicate that aflibercept is also effective in the management of PDR in the first year, allowing the use of a single drug to address both of these sight-threatening complications of diabetes.

The robust randomised controlled trial design, high statistical power, and excellent retention rates are particular strengths of this study. The study patients are representative of a PDR population, and therefore these findings can be generalised to clinical practice for the first year of therapy. Retreatment criteria used in CLARITY are very similar to those followed in the ranibizumab trial[10] and decided by treating investigators at each study visit. Compliance with treatment (94% aflibercept group and 97% PRP group) was very good in CLARITY, indicating that these retreatment criteria can be easily applied to routine clinical practice. The safety evaluation of aflibercept in CLARITY revealed no new concerns. There were no differences in Anti-Platelet Trialists' Collaboration events or other systemic adverse events between arms.

The limitation of this study is that it was a phase 2b study with follow-up for only 52 weeks. To date, the only other well designed study on anti-VEGF for PDR included patients with diabetic macular oedema and so the treatment regimen was preplanned to be more intense than this study.[10] However, as a 5 year study,

it will provide long-term outcomes of ranibizumab in PDR, information about the disease-modifying effect of anti-VEGF, and the long-term compliance of patients.

In conclusion, this is the second study to show non-inferiority of anti-VEGF to PRP and the first study to show potential advantage in best corrected visual acuity versus PRP with an anti-VEGF agent, in this case aflibercept. The study also shows that patients prefer anti-VEGF to PRP in a clinical trial setting. However, longer-term studies are required to assess long-term patient compliance and the disease-modifying effect of different anti-VEGF agents in patients with PDR in phase 3 clinical trials and in the real-life setting.

Contributors

The study was conceived by the chief investigator (SS) and co-lead (PH). The study was designed by the grant co-applicants (SS, PH, ATP, JK, CM, RT-E, JB, PH, and DH). King's Clinical Trial Unit core team: AR, JK, CM, and AR (trial manager). AP and JCV provided statistical input. SS drafted the manuscript and all authors commented on drafts and approved the final version. The Clinical Trials Manufacturing and Supplies Department, Pharmacy Production Department, and Royal Free Hospital NHS Foundation Trust, was responsible for packaging, labelling, and for a qualified person releasing the drug before distribution to site.

The CLARITY Study Group

Co-ordinators of the trial: A Bhatnagar (Wolverhampton Eye Infirmary, New Cross Hospital, Wolverhampton, UK); B Burton (Department of Ophthalmology, James Paget University Hospital, Great Yarmouth, UK); U Chakravarthy (Institute of Clinical Science, Centre for Experimental Medicine, Queen's University, Belfast, UK); H Eleftheriadis (Department of Ophthalmology, King's College Hospital NHS Foundation Trust, London, UK); T Empeslidis (Department of Ophthalmology, Leicester Royal Infirmary, Leicester, UK); R Gale (Ophthalmology Department, The York Hospital, York, UK); S George (Ophthalmology Department, Hillingdon Hospitals NHS Foundation Trust, London, UK); M Habib (Sunderland Eye Infirmary, Sunderland, UK); S Kelly (Ophthalmology Department, Royal Bolton Hospital NHS Trust, Bolton, UK); A Lotery (Faculty of Medicine, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK); M McKibbin (Ophthalmology Department, St James's University Hospital, Leeds Teaching Hospital NHS Trust, Leeds, UK); L Membrey (Department of Ophthalmology, Maidstone Hospital, Maidstone & Tunbridge Wells NHS Trust, Kent, UK); G Menon (Ophthalmology Department, Frimley Park Hospital NHS Foundation Trust, Surrey, UK); B Mushtaq (Birmingham and Midland Eye Centre, City Hospital, Birmingham); L Nicholson, J Ramu (National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust, London, UK); O Osoba (Ophthalmology Department, Torbay Hospital, Devon, UK); J Patel (Ophthalmology Department, Essex County Hospital, Colchester, UK); P Prakash (Princess Alexandra Hospital, Harlow); R Purbrick (Sussex Eye Hospital, Brighton, UK); A Ross (Bristol Eye Hospital, Bristol, UK); A Stylianides (St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, UK); J Talks (Royal Victoria Infirmary, Newcastle upon Tyne, UK). *Leads of the UK Readng Centre:* U Chakravarthy (Institute of Clinical Science, Centre for Experimental Medicine, Queen's University, Belfast, UK); S Harding (Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK); T Peto (UK Network of Reading Centres, Belfast, UK). *Lead of the Centre for Health Economics:* S T Yeo (Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK). *Trial steering committee:* Alistair Laidlaw (chairman; Guy's and St Thomas' NHS Foundation Trust, London, UK); Winfried Amoaku (University Hospital, Queen's Medical Centre, University of Nottingham, Nottingham, UK); Gillian Hood (National Institute for Health Research, Clinical Research Network, London, UK); Graham A Hitman (Barts and The London School of Medicine and Dentistry, London, UK); and Daniel Preece and Paul Burns (lay representatives). *Data monitoring committee:* Sarah Walker (chairman; Medical Research Council, Clinical Trials Unit, University College London, UK), Evelyn Mensah (Central Middlesex NHS Trust, London, UK), and Niral Karia (Southend NHS Trust, Westcliff-on-Sea, UK).

Declaration of interest

SS has received research grants, travel grants, speaker fees, and were advisory board members of Novartis, Bayer, Allergan, and Roche. PH has received research grants, travel grants, speaker fees, and were advisory board members of Novartis, Bayer, and Allergan. All other authors declare no competing interests.

Acknowledgments

The CLARITY Study Group thanks all the patients who participated in the study, and the many individuals not specifically mentioned in the paper whom have supported the study. We thank Gill Lambert, Beverley White-Alao, Oliver Pressey, Negin Sarafraz-Shekary, Evangelos Georgiou, Janice Jimenez, and the team at King's College Clinical Trials Unit. We thank the Royal Free London National Health Service Foundation Trust Pharmacists and members of the independent UK Network of Ophthalmic Reading Centres for their support of the trial. We also thank the lay panel in the North East Diabetes Research Network and Richard Lane, lay representative grant coapplicant. This investigator-initiated study was funded by EME (12/66/15) and managed by the National Institute for Health Research (NIHR) on behalf of the Medical Research Council–NIHR partnership; aflibercept solution for injection was supplied by Bayer Plc (Reading, UK) in accordance with its marketing authorisation. We thank the NIHR Clinical Research Network. The research was supported by the NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, the NIHR Moorfields Clinical Research Facility, and the UK Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley, NHS Foundation Trust, and King's College London. We thank Maggie Shergill, the research manager (monitoring) and the other team members of the NIHR Evaluation Trials and Studies Coordinating Centre. This Article presents independent research supported by the NIHR. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

References

1 Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med* 2012; **366:** 1227–39.

2 Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology* 1981; **88:** 583–600.

3 Googe J, Brucker AJ, Bressler NM, et al, for the Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011; **31:** 1009–27.

4 Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol* 2009; **127:** 132–40.

5 Preti RC, Ramirez LM, Monteiro ML, et al. Contrast sensitivity evaluation in high risk proliferative diabetic retinopathy treated with panretinal photocoagulation associated or not with intravitreal bevacizumab injections: a randomised clinical trial. *Br J Ophthalmol* 2013; **97:** 885–89.

6 Subash M, Comyn O, Samy A, et al. The effect of multispot laser panretinal photocoagulation on retinal sensitivity and driving eligibility in patients with diabetic retinopathy. *JAMA Ophthalmol* 2016; **134:** 666–72.

7 Brucker AJ, Qin H, Antoszyk AN, et al, and the Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings *Arch Ophthalmol* 2009; **127:** 132–40.

8 Flynn HW Jr, Chew EY, Simons BD, et al, and The Early Treatment Diabetic Retinopathy Study Research Group. Pars plana vitrectomy in the Early Treatment Diabetic Retinopathy Study. ETDRS report number 17. *Ophthalmology* 1992; **99:** 1351–57.

9 Simunovic MP, Maberley DA. Anti-vascular endothelial growth factor therapy for proliferative diabetic retinopathy: a systematic review and meta-analysis. *Retina* 2015; **35:** 1931–42.

10 Gross JG, Glassman AR, Jampol LM, et al, Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015; **314:** 2137–46.

11 Weidle UH, Schneider B, Georges G, Brinkmann U. Genetically engineered fusion proteins for treatment of cancer. *Cancer Genomics Proteomics* 2012; **9:** 357–72.

12 Sivaprasad S, Prevost AT, Bainbridge J, et al. Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy (acronym CLARITY): a multicentre phase IIb randomised active-controlled clinical trial. *BMJ Open* 2015; **5:** e008405.

13 Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991; **98:** 786–806.

14 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.

15 White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* 2005; **24:** 993–1007.

16 White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011; **342:** d40.

17 White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. *Clin Trials* 2012; **939:** 6–407.

18 González VH, Giuliari GP, Banda RM, et al. Intravitreal injection of pegaptanib sodium for proliferative diabetic retinopathy. *Br J Ophthalmol* 2009; **93:** 1474–78.

19 Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012; **15:** 171–85.

20 Kanda A, Noda K, Saito W, Ishida S. Aflibercept Traps Galectin-1, an angiogenic factor associated with diabetic retinopathy. *Sci Rep* 2015; **5:** 17946.

21 Driver and Vehicle Licensing Agency. Visual disorders: assessing fitness to drive. https://www.gov.uk/guidance/visual-disorders-assessing-fitness-to-drive (accessed April 15, 2017).

22 Muqit MM, Wakely L, Stanga PE, Henson DB, Ghanchi FD. Effects of conventional argon panretinal laser photocoagulation on retinal nerve fibre layer and driving visual fields in diabetic retinopathy. *Eye (Lond)* 2010; **24:** 1136–42.

23 Muqit MM, Young LB, McKenzie R, et al. Pilot randomised clinical trial of Pascal TargETEd Retinal versus variable fluence PANretinal 20 ms laser in diabetic retinopathy: PETER PAN study. *Br J Ophthalmol* 2013; **97:** 220–27.

24 Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology* 2015; **122:** 2044–52.