Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial

Andrew Lotery*, Sobha Sivaprasad*, Abby O'Connell, Rosie A Harris, Lucy Culliford, Lucy Ellis, Angela Cree, Savita Madhusudhan, Francine Behar-Cohen, Usha Chakravarthy, Tunde Peto, Chris A Rogers, Barnaby C Reeves, on behalf of the VICI trial investigators†

Summary

Background In chronic central serous chorioretinopathy (CSCR), fluid accumulates in the subretinal space. CSCR is a common visually disabling condition that develops in individuals up to 60 years of age, and there is no definitive treatment. Previous research suggests the mineralocorticoid receptor antagonist, eplerenone, is effective for treating CSCR; however, this drug is not licensed for the treatment of patients with CSCR. We aimed to evaluate whether eplerenone was superior to placebo in terms of improving visual acuity in patients with chronic CSCR.

Methods This randomised, double-blind, parallel-group, multicentre placebo-controlled trial was done at 22 hospitals in the UK. Participants were eligible if they were aged 18–60 years and had had treatment-naive CSCR for 4 months or more. Patients were randomly assigned (1:1) to either the eplerenone or the placebo group by a trial statistician through a password-protected system online. Allocation was stratified by best-corrected visual acuity (BCVA) and hospital. Patients were given either oral eplerenone (25 mg/day for 1 week, increasing to 50 mg/day for up to 12 months) plus usual care or placebo plus usual care for up to 12 months. All participants, care teams, outcome assessors, pharmacists, and members of the trial management group were masked to the treatment allocation. The primary outcome was BCVA, measured as letters read, at 12 months. All outcomes apart from safety were analysed on a modified intention-to-treat basis (participants who withdrew consent without contributing a post-randomisation BCVA measurement were excluded from the primary analysis population and from most secondary analysis populations). The trial is registered with ISRCTN, ISRCTN92746680, and is completed.

Findings Between Jan 11, 2017, and Feb 22, 2018, we enrolled and randomly assigned 114 patients to receive either eplerenone (n=57) or placebo (n=57). Three participants in the placebo group withdrew consent without contributing a post-randomisation BCVA measurement and were excluded from the primary outcome analysis population. All patients from the eplerenone group and 54 patients from the placebo group were included in the primary outcome. Modelled mean BCVA at 12 months was 79·5 letters (SD 4·5) in the placebo group and 80·4 letters (4·6) in the eplerenone group, with an adjusted estimated mean difference of 1·73 letters (95% CI –1·12 to 4·57; p=0·24) at 12 months. Hyperkalaemia occurred in eight (14%) patients in each group. No serious adverse events were reported in the eplerenone group and three unrelated serious adverse events were reported in the placebo group (myocardial infarction [anticipated], diverticulitis [unanticipated], and metabolic surgery [unanticipated]).

Interpretation Eplerenone was not superior to placebo for improving BCVA in people with chronic CSCR after 12 months of treatment. Ophthalmologists who currently prescribe eplerenone for CSCR should discontinue this practice.

Funding Efficacy and Mechanism Evaluation Programme, and National Institute for Health Research and Social Care.

Introduction

Central serous chorioretinopathy (CSCR) is the fourth most common retinal disease after neovascular age-related macular degeneration, diabetic macular oedema, and retinal venous occlusion.[1] Ten per 100 000 men and two per 100 000 women in the population develop CSCR each year.[2] The condition is characterised by subretinal fluid (SRF) accumulation, which results in central visual disturbance when located subfoveally. CSCR is frequently bilateral and most patients exhibit signs of CSCR in both eyes.[3] In most patients, the first episode of CSCR resolves spontaneously within 3 months of onset. When SRF persists beyond 3 months, the condition is considered to be chronic and can lead to permanent vision loss in up to a third of patients.[4] CSCR can occur in families and some genetic associations have been reported.[5–8]

Little progress has been made in understanding CSCR since it was first described in 1866.[9] Various treatments

Research in context

Evidence before this study

Little progress has been made in treating patients with central serous chorioretinopathy (CSCR) over the past 150 years. Our proposal to do the VICI trial was based on a literature review of possible treatments for CSCR that found no conclusive evidence supporting the effectiveness of postulated treatments in studies published between March, 1969, and January, 2010. Our search identified articles in MEDLINE that were indexed with medical subject headings (MeSH) for CSCR, chorioretinopathies, and central serous retinopathies. We restricted the search using the following MeSH subheadings: "pathophysiology of central serous chorioretinopathy", "treatment of central serous chorioretinopathy", and "photodynamic treatment in central serous chorioretinopathy". We searched for additional studies from the reference lists of included articles and review articles. In addition, we searched the ClinicalTrials.gov database for relevant studies using the same search terms. A few small phase 1 studies of aflibercept, photodynamic laser therapy, and eplerenone were identified, but we found no definitive statistically powered studies. The available studies were not large enough to detect a clinically important benefit in visual acuity (ie, of five or more letters). Consequently, the standard of care given to patients with CSCR varies. Photodynamic laser therapy and eplerenone are the most frequent treatments offered to affected patients.

Added value of this study

The VICI trial is the first randomised, double-blind, placebo-controlled trial with adequate power to detect a clinically

important improvement in visual acuity in treating CSCR with eplerenone. Visual acuity is a functional outcome of key relevance to patients with CSCR. This outcome contrasts with the primary outcome of two of three previous trials of eplerenone that instead prioritised structural changes in the retina. In the VICI trial, neither the primary or the secondary outcomes, including time-to-resolution of CSCR or recurrence of CSCR after resolution, found any benefit of eplerenone treatment over placebo. By virtue of its size, the VICI trial also provides the most comprehensive report of adverse events compared with other placebo-controlled trials. Instances of hyperkalaemia, a known adverse effect of eplerenone, arose in as many patients taking placebo as in those taking eplerenone.

Implications of all the available evidence

The VICI trial found no evidence of a clinically important benefit of eplerenone for the treatment of CSCR. This result is an important outcome that will change clinical practice, as eplerenone is commonly used by ophthalmologists as a first-line treatment for CSCR. The trial results should prompt ophthalmologists to stop using eplerenone to treat patients with CSCR and encourage patients to participate in future trials of other potential interventions.

have been used to treat CSCR despite scarce high-quality evidence to support their effectiveness. Verteporfin photodynamic laser therapy (vPDT) is used to treat some patients with CSCR. Randomised controlled trials of half-dose vPDT have shown some encouraging results in the short term.[10,11] However, most hospitals do not have access to this treatment, as it requires a specialised laser. In addition, verteporfin is not licensed for the treatment of CSCR and it is expensive. Other types of laser treatments have been tried but there is scarce evidence to support their effectiveness and no randomised placebo-controlled trials have been done to test their efficacy.[10,12,13]

Advances in retinal imaging have shown that eyes with CSCR have a thickened choroid and dilated choroidal vessels. In addition, previous studies[14,15] suggest that CSCR is associated with choroidal hyperpermeability. In a rat model of CSCR, choroidal vasodilation was induced by aldosterone (a mineralocorticoid receptor activator) acting via an endothelial vasodilatory potassium channel, known as KCa2.3. Inhibition of this pathway prevented aldosterone-induced choroidal thickening, suggesting that mineralocorticoid receptor activation might contribute to the pathogenesis of CSCR.[16] Subsequently, case series of patients with chronic CSCR who were given

oral mineralocorticoid receptor antagonists, such as eplerenone (a specific antagonist licensed for use in patients with heart failure) and spironolactone (a non-specific antagonist), have reported resolution of SRF, a reduction in choroidal thickening, and improvements in visual acuity in the short term.[17] A 2019 meta-analysis[18] of randomised trials of mineralocorticoid receptor antagonists in patients with CSCR found that these drugs provided a modest improvement in visual acuity. These results suggest that inhibiting mineralocorticoid receptors could be therapeutically beneficial for patients with CSCR. As CSCR predominantly affects men, eplerenone has been the preferred treatment option to spironolactone because the adverse effect of gynaecomastia is less prevalent with eplerenone.[19]

Despite few clinical trial data, mineralocorticoid receptor antagonists are widely used by ophthalmologists as a first-line therapy for the treatment of CSCR. As these drugs can have serious systemic side-effects, such as hyperkalaemia, it is important to determine the efficacy and safety profile of mineralocorticoid receptor antagonists. Therefore, we conducted an adequately powered, randomised, double-blind, placebo-controlled trial to assess the efficacy and safety of eplerenone for treating patients with CSCR.

Methods

Study design and participants

The VICI trial was a randomised, placebo-controlled, parallel-group, superiority trial done in 22 UK National Health Service secondary care hospitals (appendix pp 5–6). Patients with chronic CSCR attending outpatient ophthalmology clinics were screened in two stages: first by consulting patient medical records, and second, if

Figure 1: Trial profile
*Reasons for patients being excluded before randomisation are detailed in the appendix (p 69). †Three participants in the placebo group withdrew consent without contributing a post-randomisation best-corrected visual acuity measurement and were excluded from the primary outcome analysis population and from most secondary endpoints analysis populations (see appendix p 92 for the number of patients analysed for each outcome).

patients were initially eligible and after patient consent was obtained, trial-specific assessments were done to determine eligibility according to additional criteria. Eligibility was decided by experienced ophthalmologists, and patient consent was obtained by ophthalmologists or experienced research nurses.
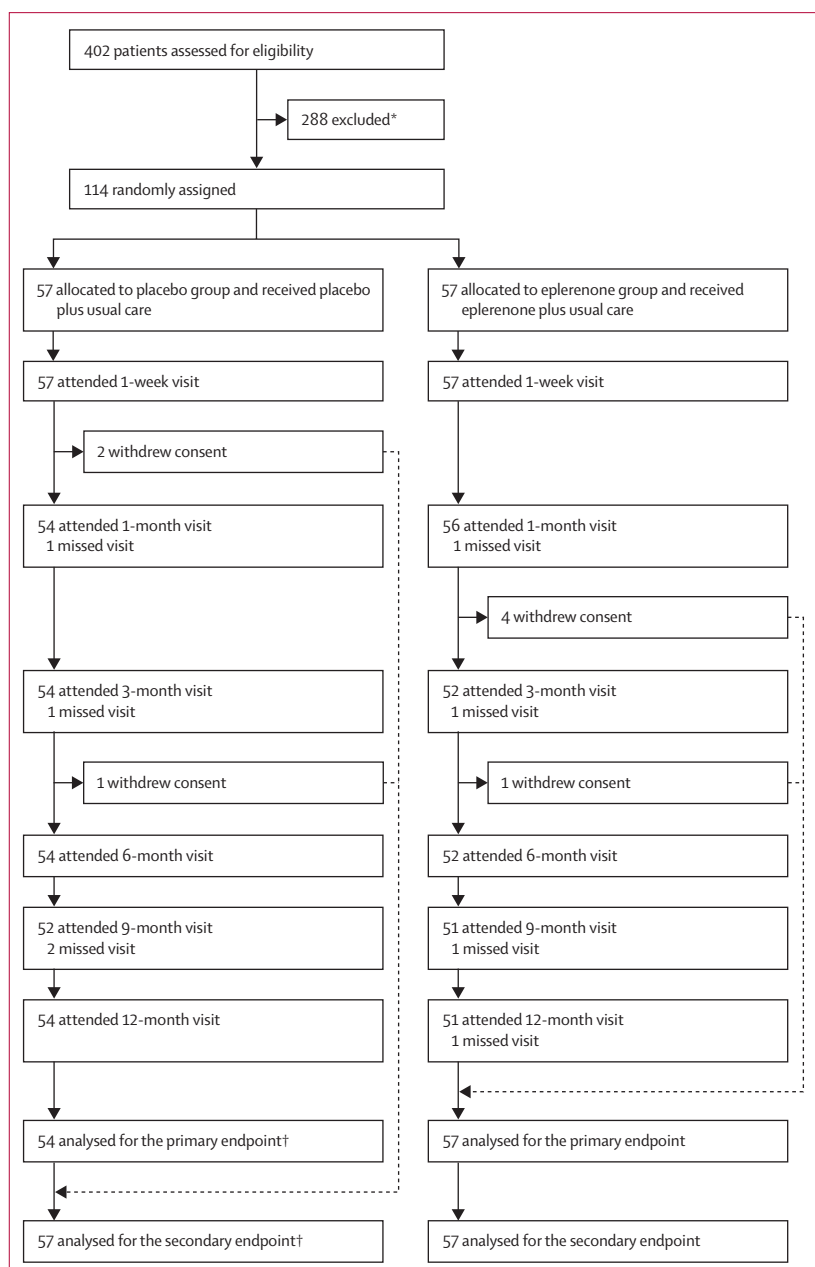
Eligibility criteria for the VICI trial have been described previously.[20] In brief, patients aged 18–60 years with treatment-naive CSCR for 4 months or more were eligible for inclusion. Patients were excluded if they had choroidal neovascularisation or any other disease that could affect visual acuity or cause retinal fluid or SRF to accumulate, myopia (–6 dioptres or worse), or hyperkalaemia (blood serum potassium of >5·0 mmol/L).

All participants provided written informed consent. The trial was sponsored by University Hospitals Southampton National Health Service Trust and was approved by the Wales Research Ethics Committee (16/WA/0069) and the Medicines and Healthcare products Regulatory Agency (EudraCT 2016-000113-70). The protocol has been published.[20]

Randomisation and masking

Participants were randomly assigned (1:1) to receive either eplerenone plus usual care or placebo plus usual care. Usual care was included in both groups to ensure participants could receive additional treatments, administered at the clinician's discretion, if necessary. Randomisation was blocked (random block sizes of two and four) and stratified by hospital and visual acuity (low [54–67 letters] or high [68–85 letters], read on an Early Treatment Diabetic Retinopathy Study [ETDRS] chart). The group allocation list was generated by the trial statistician using Stata 14.0 (StataCorp, College Station, TX, US) before patients were recruited, and the list was supplied to Newcastle Specials Pharmacy Production Unit (Newcastle upon Tyne, UK). This pharmacy was responsible for over-encapsulating eplerenone tablets, manufacturing identical placebo capsules, packaging capsules in plastic bottles, and labelling the bottles identically as clinical trial investigational medicinal products (IMPs). Each bottle was labelled with a unique number to assign bottles of IMP to participants according to their allocated group so that masking could be maintained. Production pharmacists had no role in the conduct or design of the trial. Participants, clinical teams, outcome assessors, hospital pharmacists, and the trial management group were all masked to group assignment. Unmasking was permitted only if administration of emergency treatment was required and only if permission from AL or SS was obtained. Unmasking was done by use of a secure internet-based IMP management system (IMP-Track version 1.0) or, in the event of internet failure, by code-break envelopes located in hospital pharmacies.[20,21]

Before randomisation, information to identify the participant and confirm their eligibility was entered into a secure internet-based randomisation system

(GeneSYS version 1.3.1,[22] Bristol Trials Centre, Clinical Trials and Evaluation Unit, Bristol, UK), which was only accessible to approved trial personnel. Ophthalmologists or research nurses received a bottle number assigning participants to the trial groups within 4 weeks of screening and remained successfully masked throughout the trial. The randomisation system provided the bottle number to be dispensed.

Procedures

Participants in the eplerenone group were prescribed oral 25 mg/day eplerenone for the first week, increasing to 50 mg/day for up to 12 months if blood serum potassium levels were 5·0 mmol/L or lower. Participants allocated to the placebo group followed the same treatment schedule to maintain masking. Capsules were taken orally with no restrictions on time of day or food consumption. Participants were followed up at 1 week, and at 1, 3, 6, 9, and 12 months (appendix p 70).[20] Sufficient capsules were dispensed at each visit to last until the next follow-up visit. Participants returned unused capsules at each follow-up visit, and the difference between the expected and actual number of capsules returned was calculated considering the length of time between visits. Participants were classified as adherent if more than 70% of the capsules that they had been prescribed between follow-up visits were taken. Participants stopped taking the study drug if SRF had completely resolved at any follow-up visit, but treatment was re-started if SRF recurred at a subsequent follow-up visit. If the study drug was re-started, the same dose escalation procedure was followed. If serum potassium levels exceeded 5·0 mmol/L at any follow-up visit, the study drug was stopped permanently, and the participant was invited to continue attending follow-up visits up to the end of the 12-month period.

We used a custom-designed database (GeneSYS)[22] to collect the data . The database allowed: (1) trial personnel to enter participant data at each site and to review and correct data queries; and (2) the central trial team to monitor the accrual of data centrally. We used a separate software application (IMP-Track version 1.0) to manage the distribution, tracking, and accounting of the IMP over the duration of the study.[21]

Outcomes

The primary outcome was best-corrected visual acuity (BCVA) at 12 months, as measured by use of ETDRS charts according to a standard protocol for medical retina trials.[20,23] BCVA was measured at all follow-up visits (except at week 1) by accredited optometrists at each site who were masked to BCVA results from previous visits and the participant's group allocation. Optometrists were certified to perform BCVA assessments in clinical trials during site set up.

Secondary outcomes were: low-luminance BCVA; central subfield retinal thickness; changes in SRF thickness from baseline; systemic and ocular adverse events; macular atrophy of the retinal pigment epithelium; subfoveal choroidal thickness; choroidal permeability; time-to-resolution of SRF; classification of SRF resolution

	Placebo group (n=57)	Eplerenone group (n=57)	Total (n=114)
Non-ocular history			
Age at randomisation, years	49·9 (7·9)	47·4 (7·1)	48·7 (7·6)
Male	43/57 (75%)	42/57 (74%)	85/114 (75%)
Ethnicity			
White	53/57 (93%)	46/57 (81%)	99/114 (87%)
Asian	4/57 (7%)	9/57 (16%)	13/114 (11%)
Mixed	0	1/57 (2%)	1/114 (1%)
Other	0	1/57 (2%)	1/114 (1%)
Systolic blood pressure, mm Hg*	132 (125·0–146·0)	129 (121·0–141·0)	130 (122·0–144·0)
Diastolic blood pressure, mm Hg*	80 (75·0–88·0)	80 (72·5–88·5)	80 (73·0–88·0)
Heart rate, beats per minute*	68 (60·0–76·0)	73 (66·0–80·0)	72 (63·0–78·0)
Potassium, mmol/L	4 (0·3)	4 (0·4)	4 (0·3)
Smoking status			
Current smoker	10/57 (18%)	12/57 (21%)	22/114 (19%)
Previous smoker	16/57 (28%)	25/57 (44%)	41/114 (36%)
Never smoker	31/57 (54%)	20/57 (35%)	51/114 (45%)
Heart failure	0	0	0
Myocardial infarction	1/57 (2%)	0	1/114 (1%)
History of angina	0	0	0
No angina†	57/57 (100%)	57/57 (100%)	114/114 (100%)
New York Heart Association Functional Classification			
0	56/57 (98%)	57/57 (100%)	113/114 (99%)
I	1/57 (2%)	0	1/114 (1%)
Transient ischaemic attack	0	0	0
Exposure to steroids	15/57 (26%)	12/57 (21%)	27/114 (23%)
Oral	1/15 (7%)	1/12 (8%)	2/27 (7%)
Inhaled	4/15 (27%)	6/12 (50%)	10/27 (37%)
Intramuscular injection	3/15 (20%)	0	3/27 (11%)
Topical cream	5/15 (33%)	8/12 (67%)	13/27 (48%)
Other	4/15 (27%)	1/12 (8%)	5/27 (18%)
Ocular history			
Central subfield retinal thickness duration, months	9 (6·0–18·0)	8 (6·0–22·0)	9 (6·0–19·0)
Family history of central serous chorioretinopathy	1/57 (2%)	0	1/114 (1%)
Visual acuity score			
Low (54–67)	7/57 (12%)	7/57 (12%)	14/114 (12%)
High (68–85)	50/57 (88%)	50/57 (88%)	100/114 (88%)
Best-corrected visual acuity score	78 (73·0–82·0)	77 (73·0–80·0)	78 (73·0–81·0)
Low luminance visual acuity score‡	64 (57·0–67·0)	57 (50·0–64·0)	60 (52·5–65·0)
Choroidal thickness, μm§	461 (381·5–534·5)	447 (398·0–509·0)	447 (389·0–521·0)
Subretinal fluid thickness, μm	119 (88·0–178·0)	147 (93·0–196·0)	134 (90·0–194·0)
Central subfield retinal thickness, μm	322 (280·0–394·0)	360 (290·0–406·0)	349 (280·0–401·0)
Macular atrophy of retinal pigment epithelium	3/55 (5%)	2/56 (4%)	5/111 (5%)

Data are mean (SD), median (IQR), or n/N (%). *Missing data for one patient in the eplerenone group. †According to the Canadian Cardiovascular Society grading of angina pectoris. ‡Missing data for one patient in each group. §Missing data for one patient in the placebo group.

Table 1: **Baseline patient characteristics**

as complete, partial, or none; classification of SRF resolution as early, late, or none; time-to-recurrence of SRF; fundus fluorescein angiography phenotype; incidence of CSCR in the fellow eye; and patient-reported visual function. Outcome measurements and timepoints are detailed in the appendix (pp 48–49). All retinal images were graded by masked, trained, and quality-assured independent graders from the Network of Ophthalmic Reading Centres UK.

For more on the **Network of Ophthalmic Reading Centres UK** see http://www.networcuk.com/
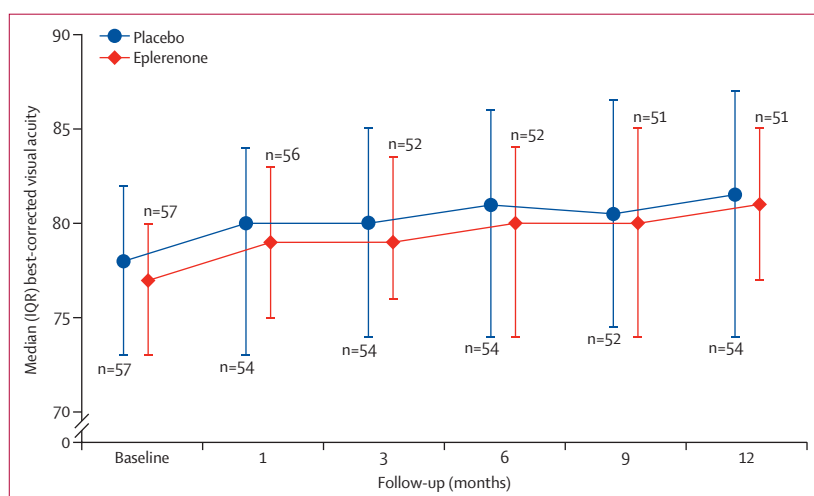
Adverse events and reactions were recorded throughout the 12-month follow-up period. General practitioners were notified by recruiting hospitals using a template letter approved by the research ethics committee if their patient was a trial participant, and practitioners were asked to inform the local research team about any suspected adverse events or reactions to the drug. At each follow-up visit participants were asked to report any adverse events since the previous visit. All adverse events were recorded on a form that categorised them by the Medical Dictionary for Regulatory Activities system organ class (version 14.1; appendix p 35).[20]

Statistical analysis

A target sample size of 104 patients was chosen for the trial to have 90% power to detect a difference of five or more letters between the two groups (two-tailed test at an α level of 0·05) assuming that less than 15% of participants would drop out during the follow-up period. The following assumptions were made: one study eye per participant; a SD of nine letters; a correlation coefficient of 0·5 between BCVA measured at baseline and at any follow-up assessment; a minimum of two follow-up assessments per participant, with a correlation coefficient of 0·8 between BCVA measured at follow-up assessments.

Analyses were directed by a prespecified statistical analysis plan (appendix pp 46–67) and done on a modified intention-to-treat basis (ie, participants who withdrew consent without contributing a post-randomisation BCVA measurement were excluded from the primary analysis population and from most secondary analysis populations [see appendix p 92 for number of

Figure 2: **Best-corrected visual acuity over 12-month follow-up period**
Mean difference at 12 months was 1·73 (95% CI –1·12 to 4·57), p=0·236.

	Placebo group (n=57)	Eplerenone group (n=57)	MD or HR (95% CI)	p value
Primary outcome				
Best-corrected visual acuity at 12 months	79·5 (4·5)	80·4 (4·6)	MD 1·73 (–1·12 to 4·57)	0·236
Secondary outcomes				
Low luminance visual acuity at 12 months	65·3 (3·7)	63·9 (4·8)	MD 0·61 (–3·79 to 5·02)	0·785
Central subfield retinal thickness at 12 months, μm	270·0 (38·0)	302·1 (43·7)	MD 24·35 (–7·86 to 56·56)	0·142
Subretinal fluid thickness at 12 months, μm*	72·5 (6·2)	120·7 (6·0)	MD 48·08 (13·43 to 82·73)	0·0066
Macular atrophy of the retinal pigment epithelium at 12 months	3/53 (6%)	4/49 (8%)	..	..
Change in area of macular retinal pigment epithelium hypoautofluorescence at 12 months, mm²†	0·03 (0·03 to 0·04)	0·72 (–0·73 to 2·10)	..	..
Choroidal thickness at 12 months, μm*	451·4 (78·6)	478·0 (58·1)	MD 38·53 (12·31 to 64·74)	0·0040
Reduced choroidal permeability at 12 months	3/54 (6%)	1/49 (2%)	..	..
Visual function questionnaire-25 overall composite score at 12 months*	89·1 (4·4)	86·5 (5·3)	MD 2·39 (–5·45 to 0·68)	0·127
Estimated median time to complete resolution of subretinal fluid, days‡	458·2 (214·1 to 702·2)	603·3 (313·1 to 893·5)	HR 0·78 (0·41 to 1·51)	0·463
Estimated median time to complete or partial resolution of subretinal fluid, days‡	184·2 (122·3 to 246·0)	141·1 (57·9 to 224·4)	HR 1·23 (0·75 to 2·01)	0·418
Estimated median time to recurrence of subretinal fluid, days‡§	192·1 (136·6 to 247·6)	182·5 (117·7 to 247·3)	HR 1·10 (0·45 to 2·66)	0·836
New central serous chorioretinopathy in the fellow eye	4/57 (7%)	5/57 (9%)	..	..

Data are presented as median (IQR), mean (SD), or n/N (%). Formal statistical comparisons of treatment effects were not done if ten or fewer patients in total did not experience or achieve the outcome. MD=mean difference. HR=hazard ratio. Total numbers of patients analysed for each outcome are listed in the appendix (p 92). *Multiple imputation (ten imputed datasets) was used to account for missing data. †Not formally tested, as only eight patients from both groups had macular retinal pigment epithelium hypoautofluorescence at baseline, at 12 months, or at both time points. ‡Median time to resolution or recurrence predicted from an interval-censored survival model. §Assumed that resolution occurred in the middle of the interval between the visit when the resolution status was negative and the first visit when the resolution status was positive.

Table 2: **Descriptive statistics for primary and secondary outcomes**

patients analysed for each outcome]). Continuous data are summarised by the mean (SD) or median (IQR) if distributions were skewed, and categorical data are reported as a number and percentage. Linear regression was used to compare continuous outcomes, proportional hazards parametric survival models were used for interval-censored data (time-to-event outcomes), and mixed effects regression was used for continuous longitudinal outcomes. Standard methods and transformations were used to assess model fit; however, alternative methods of assessment were sought if model fit was inadequate. Analyses were adjusted for the stratification factors of baseline visual acuity (54–67 letters vs 68–85 letters) fitted as a fixed effect and centre-fitted as a random effect. Centres with a small number of participants were combined to to ensure that the treatment-effect of interest could be estimated reliably (appendix p 77). For time-to-event outcomes, a clustered sandwich estimator was used to adjust the SEs for clustering within centres, as it was not possible to fit

	Placebo (n=57)				Eplerenone (n=57)			
	All events		Serious adverse events		All events		Serious adverse events	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Any event (anticipated or unanticipated)	31 (54%)	72	3 (5%)	3	30 (53%)	95	0	0
Anticipated ocular events in study or non-study eyes*†								
Study eye events	0	0	0	0	0	0	0	0
Decrease in visual acuity of ≥15 letters	0	0	0	0	0	0	0	0
Incident choroidal neovascularisation	0	0	0	0	0	0	0	0
Non-study eye events	0	0	0	0	1 (2%)	2	0	0
Decrease in visual acuity of ≥15 letters	0	0	0	0	1 (2%)	1	0	0
Incident choroidal neovascularisation	0	0	0	0	1 (2%)	1	0	0
Anticipated systemic events‡								
Infections and infestations	3 (5%)	4	0	0	8 (14%)	10	0	0
Infection	3 (5%)	4	0	0	8 (14%)	10	0	0
Pharyngitis	0	0	0	0	0	0	0	0
Pyelonephritis	0	0	0	0	0	0	0	0
Eosinophilia	0	0	0	0	0	0	0	0
Hypothyroidism	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders	9 (16%)	9	0	0	8 (14%)	8	0	0
Dehydration	0	0	0	0	0	0	0	0
Hypercholesterolaemia	1 (2%)	1	0	0	0	0	0	0
Hyperkalaemia	8 (14%)	8	0	0	8 (14%)	8	0	0
Hypertriglyceridaemia	0	0	0	0	0	0	0	0
Hyponatraemia	0	0	0	0	0	0	0	0
Insomnia	0	0	0	0	0	0	0	0
Nervous system disorders	8 (14%)	10	0	0	7 (12%)	9	0	0
Dizziness	3 (5%)	3	0	0	4 (7%)	4	0	0
Headache	6 (11%)	7	0	0	3 (5%)	5	0	0
Hypoaesthesia	0	0	0	0	0	0	0	0
Syncope	0	0	0	0	0	0	0	0
Cardiac disorders	2 (4%)	2	1 (2%)	1	3 (5%)	5	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0
Left ventricular failure	0	0	0	0	0	0	0	0
Myocardial infarction	1 (2%)	1	1 (2%)	1	0	0	0	0
Tachycardia	1 (2%)	1	0	0	3 (5%)	5	0	0
Vascular disorders	0	0	0	0	0	0	0	0
Arterial thrombosis limb	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	0	0	0	0	0

(Table 3 continues on next page)

	Placebo (n=57)				Eplerenone (n=57)			
	All events		Serious adverse events		All events		Serious adverse events	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events	Number of patients (%)	Number of events	Number of patients (%)	Number of events
(Continued from previous page)								
Cough	2 (4%)	2	0	0	3 (5%)	3	0	0
Gastrointestinal disorders	6 (11%)	10	0	0	9 (16%)	19	0	0
Constipation	0	0	0	0	1 (2%)	1	0	0
Diarrhoea	2 (4%)	3	0	0	2 (4%)	2	0	0
Flatulence	0	0	0	0	1 (2%)	1	0	0
Nausea	5 (9%)	7	0	0	4 (7%)	7	0	0
Vomiting	0	0	0	0	4 (7%)	8	0	0
Skin and subcutaneous tissue disorders	1 (2%)	1	0	0	5 (9%)	5	0	0
Angioedema	0	0	0	0	0	0	0	0
Hyperhidrosis	0	0	0	0	1 (2%)	1	0	0
Pruritus	0	0	0	0	2 (4%)	2	0	0
Rash	1 (2%)	1	0	0	2 (4%)	2	0	0
Musculoskeletal and connective tissue disorders	5 (9%)	8	0	0	11 (19%)	11	0	0
Back pain	2 (4%)	3	0	0	3 (5%)	3	0	0
Muscle spasms	0	0	0	0	1 (2%)	1	0	0
Musculoskeletal pain	5 (9%)	5	0	0	7 (12%)	7	0	0
Renal impairment	0	0	0	0	0	0	0	0
Cholecystitis	0	0	0	0	0	0	0	0
Gynaecomastia	0	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	0	2 (4%)	2	0	0
Asthenia	0	0	0	0	1 (2%)	1	0	0
Malaise	0	0	0	0	1 (2%)	1	0	0
Investigations	0	0	0	0	1 (2%)	1	0	0
Increased blood creatinine	0	0	0	0	1 (2%)	1	0	0
Increased blood glucose	0	0	0	0	0	0	0	0
Increased blood urea	0	0	0	0	0	0	0	0
Decreased epidermal growth factor receptor	0	0	0	0	0	0	0	0
Any anticipated event§	25 (44%)	46	1 (2%)	1	28 (49%)	75	0	0
Any unanticipated event§	16 (28%)	26	2 (4%)	2	13 (23%)	20	0	0

*Anticipated ocular events were specified in the protocol and were not coded using the Medical Dictionary for Regulatory Activities system organ class; they were recorded for both designated study eyes and non-study eyes. †At baseline, participants were assigned a study eye, which was defined as either the only eye with chronic serous chorioretinopathy or, if both eyes had the disease, the eye with worse disease; the other eye was classified as the non-study eye. ‡Anticipated systemic events were coded according to the Medical Dictionary for Regulatory Activities system organ class. §Some patients had both anticipated and unanticipated events and appear in both rows; therefore, the sum of the numbers of patients with any anticipated and any unanticipated event will be greater than the number of patients with any event (anticipated or unanticipated).

Table 3: Ocular and systemic adverse events

the centre as a random effect. For continuous outcomes measured at baseline and at one or more subsequent follow-up visits, baseline values were modelled as a covariate. Models for longitudinal outcomes included both time and time-by-treatment interaction terms fitted as fixed effects so that the treatment effect at 12 months could be estimated. Different variance or covariance structures were explored and the structure that provided the best fit in terms of likelihood ratio tests was used to model within patient errors. An unstructured covariance structure provided the best fit in all models. Multiple imputation (ten imputed datasets) was used to account for missing data. Placebo plus usual care was the reference group in all analyses. Likelihood ratio tests were used to determine statistical significance when possible, and results are reported as effect estimates with 95% CIs. A prespecified exploratory analysis was done to assess the effect of adherence and treatment on the primary outcome. Sensitivity analyses included adjusting time-to-event outcomes for baseline imbalances in prognostic factors and reassessing the effect of adherence and treatment on the primary outcome after

imputing pill counts for lost bottles. Two post-hoc analyses were used to: (1) re-estimate the treatment effects for BCVA, central subfield retinal thickness, SRF thickness, and choroidal thickness after adjusting for PDT administered during follow-up, and; (2) analyse choroidal thickness in the other eye.

To put our findings into context, we did a systematic review and meta-analysis of other trials that compared eplerenone with placebo. Our search identified articles in MEDLINE that were indexed with the following Medical Subject Heading terms: "central serous choroidal retinopathy" AND ("eplerenone" OR "mineralocorticoid receptor antagonists") AND ("publication type=randomized controlled trial"). We assessed the risk of bias,[24] and re-analysed data reported in the trials to identify treatment effects for BCVA and SRF thickness using the same metric (ie, the difference in the change in BCVA and SRF thickness from baseline to the end of treatment between the two groups). If it was not possible to calculate the SD of the mean change from baseline for a group, an average of the SDs from the other studies was used. The treatment effects were synthesised in a fixed-effects meta-analysis to estimate weighted mean differences (MDs) between eplerenone and placebo groups according to the inverse variance method.

Data were analysed with Stata version 15.1 (StataCorp, LP, College Station, TX, USA). Further details of the statistical analyses are provided in the statistical analysis plan (appendix pp 46–67).

The trial was overseen by an independent data monitoring and safety committee who reported their recommendations to an independent trial steering committee (appendix p 68). The trial is registered with ISRCTN, ISRCTN92746680.

Role of the funding source

The funder and the sponsor of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 402 patients were screened for inclusion and 305 were identified as initially eligible. Of the initially eligible patients, 223 were approached, and 179 consented to participate. 64 patients were subsequently identified as ineligible and one patient withdrew their consent (appendix p 69). Between Jan 11, 2017, and Feb 22, 2018, we randomly assigned 114 patients to receive either eplerenone plus usual care (57 patients) or placebo plus usual care (57 patients; figure 1).

111 patients attended at least one post-randomisation visit in which BCVA was measured. Three participants in the placebo group withdrew consent without contributing a post-randomisation BCVA measurement and were excluded from the primary analysis population and most

secondary analysis populations (appendix p 92); two participants withdrew consent after the 1-week visit, and one participant did not attend the 1-month and 3-month follow-up visits and withdrew consent after 3 months without attending any further visits. Nine scheduled follow-up visits were missed by participants who had not withdrawn their consent at the time (four visits were missed by three patients in the placebo group and five visits were missed by three patients in the eplerenone group). Adherence to taking the capsules was similar between the two groups (appendix p 76). There were no instances of a participant receiving the wrong drug and only a few instances of other protocol deviations, apart from the number of visits attended outside the prespecified visit window (62 visits by 31 patients in the eplerenone group and 53 visits by 30 patients in the placebo group; appendix pp 72–73). During follow-up, six patients in the placebo group and three patients in the eplerenone group received PDT as usual care and one participant in the placebo group received sub-threshold laser therapy as usual care (appendix p 76).

Baseline patient characteristics by group are shown in table 1. There was no difference in the median duration of treatment (time during follow-up when participants were taking their allocated capsules) between groups (9·1 months in the eplerenone group and 8·8 months in the placebo group; appendix pp 74–75).

Modelled mean BCVA at 12 months was 80·4 letters (SD 4·6) in the eplerenone group and 79·5 letters (SD 4·5) in the placebo group. On average, BCVA increased by approximately four letters in both groups during follow-up (figure 2). No difference in BCVA at 12 months between the two groups was observed (estimated MD 1·73 letters [95% CI –1·12 to 4·57]; p=0·24; table 2). The exploratory analysis found that adherence and duration of treatment had no effect on BCVA, irrespective of whether pill counts were imputed for lost IMP bottles (appendix p 93). The post-hoc analysis, which adjusted for the estimated difference in BCVA between groups for PDT administered during follow-up, did not change this result (appendix p 93).

Results for secondary outcomes and treatment effects by group are described in table 2 and the appendix (pp 78–85). There were no significant differences between groups in favour of eplerenone treatment. In addition, there were no apparent differences in the pattern of complete resolution of SRF or recurrence of CSCR (with or without adjustment for baseline SRF thickness) between the two groups (appendix p 93). Furthermore, central subfield retinal thickness at 12 months did not differ significantly between the two groups (MD 24·35 μm [95% CI –7·86 to 56·56]; p=0·14), but a significant difference in SRF thickness favouring placebo at 12 months was observed (MD 48·08 μm [95% CI –13·34 to 82·73]; p=0·0066).

Serum potassium levels were similar in both groups during follow-up (appendix p 75). Levels greater than

5·0 mmol/L prompted discontinuation of the IMP in eight (14%) participants in each group. Results for all serious adverse events and other adverse events are shown in table 3. Three serious adverse events were reported in the placebo group, and none of these events were considered to be associated with the IMP.

The results of the systematic review and meta-analysis can be found in the appendix (pp 94–98). Three trials[25–27] compared eplerenone with placebo in 40 eyes over 1 month of treatment, 21 eyes over 2 months of treatment, and 19 eyes over 3 months of treatment. The fourth trial included in the meta-analysis was the VICI trial, which analysed 111 eyes over 12 months of treatment. The pooled difference in the mean change in BCVA between the placebo and eplerenone groups was 0·06 logarithm of the minimum angle of resolution (95% CI −0·09 to −0·02; equivalent to 3·0 letters and −4·5 to −1·0 ETDRS letters; I^2 31%). The pooled difference in SRF thickness was −26·7 μm (95% CI −63·1 to 9·8; I^2 84%).

Discussion

The result for the primary outcome of the VICI trial excludes the target difference that the VICI trial was powered to detect (an upper 95% confidence limit of 4·57 letters), indicating that treatment with eplerenone did not improve BCVA by five or more letters compared with placebo at 12 months of follow-up. There was no difference in the median times to complete resolution of SRF or subsequent recurrence of CSCR, and no difference in several measurements of retinal morphology, between the two groups. Of particular note, two retinal morphology outcomes (SRF thickness and choroidal thickness) significantly favoured placebo. The reasons for these results are unclear. The findings for BCVA, time-to-event outcomes, and key morphological outcomes were unaltered in sensitivity, exploratory, or post-hoc analyses. The absence of any difference in outcomes between the eplerenone and placebo groups favouring eplerenone cannot be explained by weaknesses in trial conduct. The primary analysis included 97% of randomised patients, and overall, these patients attended 99% of all scheduled visits. In addition, there were no protocol deviations that could have affected the treatment comparison.

The results of the meta-analysis are consistent with the VICI trial results, as the point estimates for the mean change in BCVA and SRF thickness from baseline to the end of treatment in the VICI trial lie within the 95% CIs for the pooled estimates from the meta-analysis. The pooled difference in mean change in BCVA also excludes the target difference that the VICI trial was powered to detect (upper 95% confidence limit, −4·5 letters). However, the pooled differences in SRF show substantial heterogeneity, and the effect of treatment with eplerenone on SRF thickness in the VICI trial opposed the treatment effects of this drug in the other three trials included in the meta-analysis. The reason for these inconsistent results is

unclear. However, it is possible that the effect of eplerenone on SRF thickness is short-lived, and shorter follow-up intervals (eg, every 4 weeks) might have provided more data and allowed a more detailed comparison of response to treatment with eplerenone and placebo.

Notwithstanding the risk of bias assessment, we have concerns about the quality of the three small trials[25–27] included in the meta-analysis (appendix p 95). One trial[25] was not registered despite being published in 2016. We were unable to find a published protocol or prespecified analysis plan for any of the trials, and the reported analyses of treatment effects were unusual, suggesting selection of the reported result.[24] In our meta-analysis, we avoided bias from selection of the reported result by re-analysing the published data.

The VICI trial had several strengths. All but three participants contributed to the primary analysis and participants attended almost all scheduled visits. There were no protocol deviations that compromised the treatment comparisons. The trial was powered to detect a clinically important difference in BCVA; a measure that is being used by several large multicentre trials of treatments for retinal conditions. In fact, the VICI trial had more power than anticipated because participants attended almost all scheduled visits.[28,29]

Limitations of the trial included the need to discontinue treatment if CSCR resolved completely during follow-up or if an elevation in serum potassium levels was detected. Hyperkalaemia was not a common side-effect in patients included in this trial, as they were younger and fitter (ie, all but one patient was classified as class 0 according to the New York Heart Association Functional Classification system, and no patients had angina) than patients who are usually prescribed eplerenone for heart failure. These limitations might have reduced the observed treatment effect, but they were required to ensure the safety of participants. As such, we compared recurrence of CSCR after complete resolution and found no difference between the two groups. Our inability to control the use of co-treatments could have introduced bias if they were used differentially in each group (ie, if they had been administered to more patients in one group than another). Of note, more patients in the placebo group were given PDT than in the eplerenone group. However, co-treatments (including PDT) were used rarely in patients overall, and the post-hoc analysis showed that the results were not affected after adjusting for the small difference in the number of patients who were given PDT in each group.

In summary, the VICI trial found no evidence of a clinically important benefit of eplerenone for the treatment of CSCR. This result is an important outcome that will change clinical practice. The trial results should prompt ophthalmologists to stop prescribing eplerenone to treat CSCR and encourage patients to participate in future trials of other potential interventions. CSCR remains a devastating condition for people (aged 18–60 years) who

are affected, and it remains a challenging condition for ophthalmologists to manage.

References
1   Wang M, Munch IC, Hasler PW, Prunte C, Larsen M. Central serous chorioretinopathy. *Acta Ophthalmol* 2008; **86:** 126–45.
2   Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. *Eye (Lond)* 2010; **24:** 1743–56.
3   van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: towards an evidence-based treatment guideline. *Prog Retin Eye Res* 2019; published online July 15. DOI:10.1016/j.preteyeres.2019.07.003.
4   Loo RH, Scott IU, Flynn HW, Jr, et al. Factors associated with reduced visual acuity during long-term follow-up of patients with idiopathic central serous chorioretinopathy. *Retina* 2002; **22:** 19–24.
5   van Dijk EHC, Schellevis RL, Breukink MB, et al. Familial central serous chorioretinopathy. *Retina* 2019; **39:** 398–407.
6   Weenink AC, Borsje RA, Oosterhuis JA. Familial chronic central serous chorioretinopathy. *Ophthalmologica* 2001; **215:** 183–87.
7   Schellevis RL, van Dijk EHC, Breukink MB, et al. Role of the complement system in chronic central serous chorioretinopathy: a genome-wide association study. *JAMA Ophthalmol* 2018; **136:** 1128–36.
8   Hosoda Y, Yoshikawa M, Miyake M, et al. *CFH* and *VIPR2* as susceptibility loci in choroidal thickness and pachychoroid disease central serous chorioretinopathy. *Proc Natl Acad Sci USA* 2018; **115:** 6261–66.
9   Von Graefe A. Über centrale recidivrende retinitis. *Arch Klin Exp Ophthalmol* 1866; **12:** 211–15.
10 van Dijk EHC, Fauser S, Breukink MB, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the PLACE trial. *Ophthalmology* 2018; **125:** 1547–55.
11 Erikitola OC, Crosby-Nwaobi R, Lotery AJ, Sivaprasad S. Photodynamic therapy for central serous chorioretinopathy. *Eye (Lond)* 2014; **28:** 944–57.
12 Salehi M, Wenick AS, Law HA, Evans JR, Gehlbach P. Interventions for central serous chorioretinopathy: a network meta-analysis. *Cochrane Database Syst Rev* 2015; **12:** CD011841.
13 Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. *Prog Retin Eye Res* 2015; **48:** 82–118.
14 Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina* 2009; **29:** 1469–73.
15 Kim YT, Kang SW, Bai KH. Choroidal thickness in both eyes of patients with unilaterally active central serous chorioretinopathy. *Eye (Lond)* 2011; **25:** 1635–40.
16 Zhao M, Celerier I, Bousquet E, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest* 2012; **122:** 2672–79.
17 Iacono P, Toto L, Eliana C, Varano M, Parravano MC. Pharmacotherapy of central serous chorioretinopathy: review of the current treatments. *Curr Pharm Des* 2018; **24:** 4864–73.
18 Wang SK, Sun P, Tandias RM, Seto BK, Arroyo JG. Mineralocorticoid receptor antagonists in central serous chorioretinopathy: a meta-analysis of randomized controlled trials. *Ophthalmol Retina* 2019; **3:** 154–60.
19 Lainscak M, Pelliccia F, Rosano G, et al. Safety profile of mineralocorticoid receptor antagonists: spironolactone and eplerenone. *Int J Cardiol* 2015; **200:** 25–29.
20 Willcox A, Culliford L, Ellis L, et al. Clinical efficacy of eplerenone versus placebo for central serous chorioretinopathy: study protocol for the VICI randomised controlled trial. *Eye (Lond)* 2018; **33:** 295–303.
21 Bristol Trials Centre, University of Bristol. IMP-Track User Manual. Dec 14, 2018. http://cteu.bris.ac.uk/media/10067/imp-track-user-manual-v10.pdf (accessed Oct 28, 2019).
22 Hutton D, Smith N, Cappel-Porter H, Saw C, Rogers CA. Development of the "GeneSYS" database system to support trial data capture and conduct. *Trials* 2019; **14:** P66.
23 Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN). *Health Technol Assess* 2015; **19:** 1–298.
24 Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.
25 Pichi F, Carrai P, Ciardella A, Behar-Cohen F, Nucci P. Comparison of two mineralcorticosteroids receptor antagonists for the treatment of central serous chorioretinopathy. *Int Ophthalmol* 2016; **37:** 1115–25.
26 Rahimy E, Pitcher JD 3rd, Hsu J, et al. A randomized double-blind placebo-control pilot study of eplerenone for the treatment of central serous chorioretinopathy (ECSELSIOR). *Retina* 2017; **38:** 962–69.
27 Schwartz R, Habot-Wilner Z, Martinez MR, et al. Eplerenone for chronic central serous chorioretinopathy-a randomized controlled prospective study. *Acta Ophthalmol* 2017; **95:** e610–18.
28 Group CR, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364:** 1897–908.
29 Sivaprasad S, Prevost AT, Vasconcelos JC, et al. 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. *Lancet* 2017; **389:** 2193–203.