Comparative efficacy of treatments for chronic central serous chorioretinopathy: a systematic review with network meta-analyses

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REVIEW ARTICLE

Comparative efficacy of treatments for chronic central serous chorioretinopathy: A systematic review with network meta-analyses

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Abstract

Treatment of chronic central serous chorioretinopathy (cCSC) remains a topic of controversy. As cCSC is a disease that can wax and wane, treatment efficacy is difficult to assess especially when trials compare active treatments without any placebo/control group. In this study, we systematically reviewed short-term efficacies of any cCSC treatment tested in randomized controlled trials (RCT) and employed network meta-analyses to compare to non-treatment controls. We searched 11 literature databases on 20 March 2022 for RCTs of treatment of cCSC. We identified 17 RCTs including a total of 1172 eyes. Treatments included conventional laser (44 eyes), half-dose or half-fluence photodynamic therapy (PDT) (298 eyes), ranibizumab (16 eyes), antioxidants (50 eyes), mineralocorticoid receptor antagonists (187 eyes), rifampicin (91 eyes), selective retina therapy (SRT) (67 eyes) and subthreshold micropulse laser (192 eyes). Compared with controls, significant benefit on complete subretinal fluid resolution was only obtained from half-dose or half-fluence PDT (OR: 20.6; 95% CI: 6.3–66.7; $p < 0.0001$) and conventional laser (OR: 36.4; 95% CI: 2.0–655.7; $p = 0.015$), and at an order of magnitude lower degree from SRT (OR: 3.4; 95% CI: 1.7–6.8; $p = 0.00075$). Compared with controls and after sensitivity analyses, significant benefit in the change in best-corrected visual acuity was only obtained by half-dose/-fluence PDT (−0.13 logMAR; 95% CI: −0.20 to −0.06 logMAR; $p = 0.00021$). In conclusion, three treatment options provide significant improvement over no treatment: half-dose/-fluence PDT, conventional laser and to a much lesser degree SRT. Considering that conventional laser can only be applied for extrafoveal leaks, and the long-term data available for PDT-based treatments finding persisting treatment results, half-dose or half-fluence PDT is the only viable treatment option for patients with cCSC. Shortage issues with verteporfin should not lead to employment of ineffective treatment modalities, as they put patients at unnecessary risk of adverse events.

KEYWORDS
central serous chorioretinopathy, network meta-analysis, subretinal fluid, systematic review, treatment comparison

1 | INTRODUCTION

Central serous chorioretinopathy (CSC) is a relatively common cause of vision loss, which predominantly affects men aged 30–60 years (Kido et al., 2021) and is considered the fourth most common maculopathy due to central fluid leakage, after neovascular age-related macular degeneration, diabetic macula oedema and retinal venous occlusion (van Rijssen et al., 2019). A broad range of clinical pictures associated with macular subretinal fluid (SRF) can resemble CSC and can be differentiated from CSC based on thorough clinical (and sometimes genetic) analysis including multimodal imaging (van Dijk & Boon, 2021). Clinical, imaging-based and translational studies have explored CSC pathophysiology and collectively suggest the presence of a choroidopathy, visible on optical coherence tomography (OCT) as a thickened and abnormal choroid (Cheung et al., 2019; Maruko et al., 2010; Spaide et al., 2022). These enlarged, congested large choroidal vessels ('pachyvessels') may be the result of venous congestion and outflow problems at the level of the vortex veins (Cheung et al., 2019; Pang et al., 2014; Spaide et al., 2022), intervortex vein anastomoses (Spaide et al., 2021) and possibly arteriovenous anastomosis (Brinks et al., 2022). As a result, increased hydrostatic pressure from the choroid towards the retina and choriocapillaris can lead to damage to the retinal pigment epithelium (RPE), with subsequent serous detachments of the RPE (Brinks et al., 2022; Teussink et al., 2015). When the RPE outer blood–retina barrier is disrupted, SRF can accumulate, which is most easily detected on OCT. Fluorescein angiography (FA) shows focal leak(s) and pooling of fluorescein corresponding to areas of SRF. FA also reveals areas of RPE atrophy as window defects. On indocyanine green angiography (ICGA), choroidal abnormalities typical of CSC can be observed, which include the pachyvessels as well as presence of intervortex vein anastomoses. Mid-phase ICGA can also show hyperfluorescence that expands over time as a sign of choroidal vascular hyperpermeability (van Dijk & Boon, 2021). CSC can be stratified according to onset and chronicity of this SRF, for example a new case of such SRF is considered acute CSC, and a non-resolving case of CSC lasting more than 3–6 months, with atrophic RPE changes, is generally considered chronic CSC (cCSC) (van Rijssen et al., 2019). However, CSC can also be classified based on other definitions, and this remains a topic of ongoing debate (Chhablani et al., 2020, 2022). Many cases of acute CSC resolve spontaneously and can be observed without treatment (Mohabati et al., 2020; van Rijssen et al., 2019). However, cCSC should be treated as prolonged presence of SRF without treatment induces irreversible vision loss due to photoreceptor atrophy and decreased vision-related quality of life (Breukink et al., 2016; Peiretti et al., 2015; Wang et al., 2002).

One challenging aspect in the assessment of treatment efficacy in CSC is the characteristic of SRF to wax and wane even in supposedly chronic cases of CSC (van Rijssen et al., 2019). Hence, efficacy measures of CSC treatment trials can be difficult to interpret, if a non-treatment control is not included as a separate arm in a trial. For example, to the best of our knowledge no randomized controlled trial (RCT) have compared intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment to placebo/observation in cCSC. When intravitreal anti-VEGF treatment is only compared with an active treatment, it becomes unclear if cases that resolve or improve in the anti-VEGF treatment group experience a significant better outcome than the observation group, or if the study outcome simply reflects the natural course of the disease.

Network meta-analyses allow comparison of multiple treatment modalities. Using direct and indirect comparisons, treatment efficacies of all available treatments can be ranked according to a pre-defined group, such as non-treatment control, if it is possible to draw a complete network between treatment modalities (Subhi et al., 2022). This method of evidence synthesis has allowed more comprehensive reviews of treatment efficacies, where multiple treatments exist for different diseases in ophthalmology (Bicket et al., 2021; Fallico et al., 2021; Ha et al., 2022; Halili et al., 2020; Li et al., 2021; Rasmussen et al., 2022). For the case of cCSC, network meta-analyses potentially allow comparison between different treatment modalities to the natural disease course without treatment. Thus, in this systematic review, we employed network meta-analyses to evaluate and rank short-term treatment efficacies of all available treatments tested in RCTs for cCSC.

2 | METHODS

2.1 | Study design

This systematic review and network meta-analysis followed the considerations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). For all practical and analytical aspects of this study, we followed the recommendations outlined in the Cochrane Handbook (Higgins et al., 2022). The protocol was registered a priori in the PROSPERO database (no. CRD42022323230).

2.2 | Eligibility criteria and outcomes of interest

Studies were considered eligible according to the following criteria.

2.2.1 | Population

Adult patients with treatment-naïve cCSC could be included in the current study. Population being adult was defined as studies where it could be assumed based on study design and participant data that >95% of the study population was aged 18 years or above. We did not force any restrictions on the diagnostic criteria for CSC, but instead noted diagnostic approaches and definitions listed by the authors. However, we did restrict study populations to cCSC defined as either an author-defined

diagnosis of cCSC, presence of a diagnosis of CSC for at least 3 months or symptoms that could be attributable to CSC with a duration of at least 3 months. Furthermore, due to our outcome definitions, we also only evaluated studies with OCT scans of their patients. Studies without any distinction of acute versus cCSC or without specifications regarding the duration of CSC were not considered eligible, as this would introduce a significant heterogeneity to the meta-analyses due to the differences in the natural course of acute CSC versus cCSC. Studies of cCSC with macular neovascularization were not considered eligible for this review.

2.2.2 | Intervention

We considered any therapeutic intervention eligible to be considered for this review. Any intervention had to be allocated in a randomized fashion with comparison(s) to another group(s).

2.2.3 | Comparison

Comparison groups were defined as either another active treatment, placebo treatment or a non-treatment control. Studies without any data on a comparison group were not considered eligible.

2.2.4 | Outcomes

Our outcomes of interest were the complete SRF resolution on OCT, change in best-corrected visual acuity (BCVA), vision-related quality of life and any safety-related events. Outcomes were evaluated at 2 months after commencement of therapy, or any reported follow-up date closest to 2 months but within 1–3 months after commencement of therapy. All BCVA data were transformed to logarithm of the minimum angle of resolution (logMAR) for analysis.

2.2.5 | Study type

We only considered RCTs eligible for inclusion in this review. We did not enforce any restrictions based on blinding strategy, method of randomization or any other methodological characteristics. We did not restrict eligibility based on geography or journal. We only considered peer-reviewed studies disseminated in English language eligible for inclusion. Conference abstracts or non-peer-reviewed grey literature could not be included in this study.

2.3 | Information source and literature search strategy

We searched the databases PubMed/MEDLINE, EMBASE, Cochrane Central, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index and SciELO Citation Index. The search was performed on 20 March 2022 using search phrases specifically tailored to the individual databases by a trained investigator (author Y.S.). Details of the literature search for each database are outlined in Appendix S1.

2.4 | Study selection, data items and collection, and risk of bias within studies

All references extracted from the literature search were imported to EndNote X9.3.1. for Mac (Clarivate Analytics). Titles and abstracts from all identified records were examined by 1 author (Y.S.), who removed duplicates and obviously irrelevant reports. Remaining records were then retrieved in full text and examined for eligibility by two independent authors (E.H.C.D. and H.M.A.F.). Reference lists from read full-text records were checked for any additional eligible records. The authors then compared and discussed the study eligibility results with a third author (Y.S.), who had the final decision when consensus could not be reached.

We extracted data from eligible studies regarding study design, characteristics, population, intervention/comparisons and outcomes. We defined baseline as the latest visit prior to the intervention/comparison. Risk of bias within studies was evaluated using the Cochrane risk of bias tool version 2 (Sterne et al., 2019). Two authors independently extracted data from each study and performed risk of bias evaluation (E.H.C.D. and J.B.). The authors then compared and discussed the risk of bias evaluation with a third author (Y.S.), who had the final decision when consensus could not be reached.

2.5 | Data synthesis and risk of bias across studies

All studies were qualitatively reviewed in text and tables. Quantitative analyses were facilitated by network meta-analyses. For network meta-analyses, we constructed network plots to provide an overview of direct comparisons and to confirm the existence of a complete network. We used the generalized pairwise modelling approach, which is based on repeated application of adjusted indirect comparisons (Doi & Barendregt, 2018). The generalized pairwise modelling approach delivers robust results and is comparable to the Bayesian and multivariate modelling approaches (Doi & Barendregt, 2018). We used the random-effects model to account for potential heterogeneity across studies. Meta-analyses were made using MetaXL 5.3 (EpiGear International) for Microsoft Excel (Microsoft), which uses the generalized pairwise modelling framework.

Meta-analyses were made on a categorical outcome (resolution of SRF) and a continuous outcome (change in BCVA in logMAR). For the continuous outcomes, we realized that several studies did not report standard deviation (SD) in logMAR. In such cases, SDs were estimated if the standard error of the mean was reported

or otherwise based on averaged data from other studies using similar methods. Some studies only reported data from baseline and follow-up examinations, but not data on the changes in parameters between examinations. In such cases, we calculated the change by simple subtraction of means, and the SD of the change (SD_{change}) was calculated using the following formula:

$$SD_{change} = \sqrt{SD_{pre}^2 + SD_{post}^2 - \left(2 \times C \times SD_{pre}^2 \times SD_{post}^2\right)}$$

where SD_{pre} and SD_{post} are respectively the SD from pre- and post-treatment, and C the correlation coefficient which describes how similar the baseline and follow-up data were across participants (Higgins et al., 2022). Individual participant data are needed for an exact calculation of C, which is unfortunately rarely reported. To allow precise calculations, we obtained individual participant data from the SPECTRA trial (van Rijssen et al., 2022) to calculate C in a relevant study sample. Here, we calculated C to be 0.8 for the BCVA data. We therefore assumed a C of 0.8 for our meta-analysis. To explore the impact of our assumption, we also conducted a sensitivity analysis where our analysis on BCVA data was re-analysed using a C of 0.5 (i.e. moderate correlation) and a C of 0.99 (i.e. strict correlation).

Risk of bias evaluation was based on assignment to intervention (i.e. the intention-to-treat effect) and made on five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of outcome and selection of the reported results), which together contributed to an overall risk of bias evaluation.

Summary estimates were reported using odds ratio (OR) for the resolution of SRF and weighted mean difference (WMD) using change in BCVA in logMAR. Furthermore, 95% confidence intervals (95% CI) were provided for all estimates. p-Values below 0.05 were considered sign of statistical significance.

3 | RESULTS

3.1 | Study characteristics

3.1.1 | Study selection

Our search identified 984 records of which 298 were duplicates and 652 were obviously irrelevant or non-English records. The remaining 34 records were retrieved in full text for eligibility assessment. No additional records were identified by reviewing reference lists. After careful review, 20 studies were found eligible for the qualitative review and 17 for the quantitative review (Figure 1).

3.1.2 | Characteristics of eligible studies

Eligible studies summarized data on a total of 1172 eyes of patients who were recruited of which 1090 eyes remained for follow-up analysis (Figure 2). Studies reported data from participants in Asia (n = 9), Europe (n = 8), Middle East (n = 1), North America (n = 1) and South America (n = 1). Diagnosis of CSC was based on OCT in all eligible studies, while 15 studies clearly stated also to have used fluorescein angiography to demonstrate active leakage, and six studies clearly stated also to have employed ICGA for aid in diagnosis of CSC-associated findings and for differential diagnosis. Chronic CSC was defined inconsistently and using varying criteria. Eligibility criteria of individual studies and details regarding diagnostic approach and definition of cCSC are summarized in detail in Table 1.

Study groups were similar across groups in age (range of means: 40–62 years) and gender distribution, with females constituting the minority in all studies. Most studies included participants with a mean BCVA of 0.2–0.3 logMAR, although few studies also had participants with worse or better mean BCVA. Most studies included one eye par participant. The vast majority of participants allocated to a group remained in that group until the follow-up of interest for this meta-analysis. Details regarding study groups are summarized in Table 2.

Study groups in evaluation were control or placebo (10 studies, 227 eyes), half-dose PDT (six studies, 212 eyes), half-fluence or lower-fluence PDT (up to 30%) (five studies, 86 eyes), oral eplerenone (five studies, 159 eyes), subthreshold micropulse laser (SML) (five studies, 172 eyes), selective retina therapy (SRT) (three studies, 67 eyes), oral spironolactone (two studies, 28 eyes), oral rifampicin (two studies, 91 eyes), 689 nm laser therapy (i.e. a therapy based on the concept of SML) (one study, 20 eyes), intravitreal ranibizumab (one study, 16 eyes), oral lutein and antioxidants (one study, 50 eyes) and threshold conventional laser (one study, 44 eyes) (Appendix S2). Data for this review were available from follow-up at 1–3 months. Outcome data were available for evaluation of SRF resolution in 17 studies, evaluation of change in BCVA in all 20 studies, evaluation of vision-related quality of life in two studies and for safety events in 17 studies. Details of efficacy outcomes and safety events are summarized in Table 3.

3.2 | Results of individual studies

3.2.1 | Studies of laser-based therapies

Two studies compared different approaches to PDT. Park et al. (2021) randomized patients to low-fluence PDT at different percentages of standard fluence (i.e. 30% vs. 40% vs. 50%). The authors found that 50% fluence (i.e. half-fluence) PDT was significantly more effective for SRF resolution and improvement in BCVA than 40% and 30% fluence (Park et al., 2021). Cheng et al. (2017) randomized patients to either half-dose PDT or half-fluence PDT. This study reported no significant differences in BCVA, decrease in central retinal thickness on OCT, or ICGA-based evaluation of choroidal perfusion (Cheng et al., 2017).

Three studies randomized patients to either half-dose PDT or SML. Kretz et al. (2015) found that both treatment modalities led to improvement in BCVA, resolution of SRF and reduction in the overall central macular thickness on OCT. Differences between the groups were

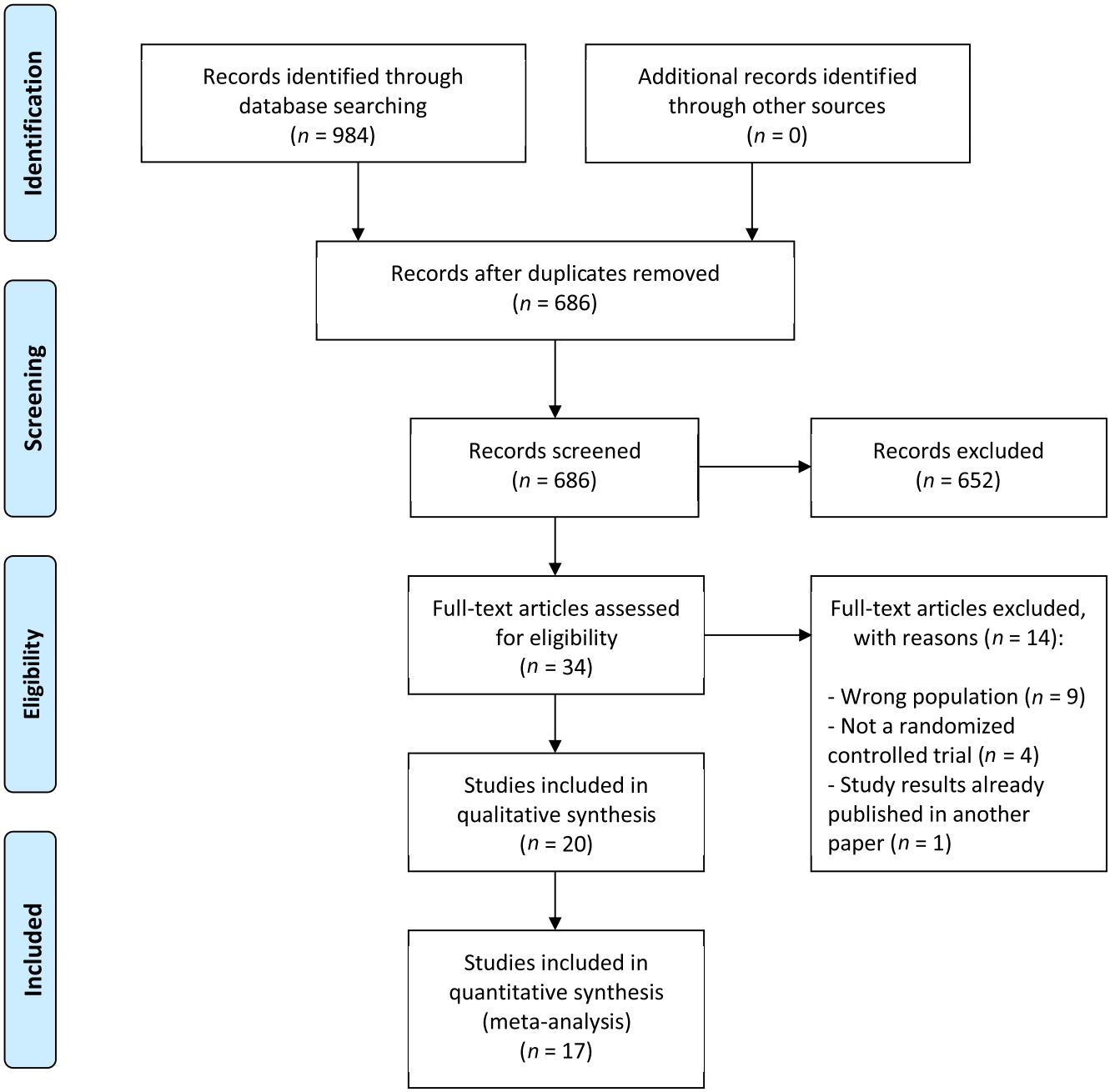

FIGURE 1 PRISMA flow diagram of study selection.

not statistically significant but were both significantly better than a third group of patients which did not undergo randomization and were followed without any treatment (Kretz et al., 2015). van Dijk et al. (2018) conducted a large multicentre trial and found that half-dose PDT was superior to SML for resolution of SRF and improvement in BCVA. Ho et al. (2021) found that both treatment modalities lead to a similar level of improvement in BCVA, but that significantly more individuals in the half-dose PDT group achieved complete resolution of SRF (Ho et al., 2021). The authors also evaluated choroidal layer changes and choriocapillaris perfusion and found that both treatment modalities lead to areas with flow deficit and changes in the choroidal volume, but that the effect of half-dose PDT was greater than that of SML.

Russo et al. (2017) randomized patients to either half-dose PDT or 689 nm laser therapy without administration of verteporfin. The authors aimed to use a near-infrared laser treatment to produce a photothermal effect to heat and stimulate the RPE (Russo et al., 2017), which is similar to the concept of SML. In their study, both groups showed improvement in BCVA and resolution of SRF, which did not differ statistically significantly after a long period of follow-up; however, the improvements came faster in the half-dose PDT group (Russo et al., 2017).

Roisman et al. (2013) randomized patients to either SML or placebo. Both groups improved in BCVA, central macular thickness and resolution of SRF at follow-up; however, the SML group was superior in terms of BCVA improvement (Roisman et al., 2013).

Sun et al. (2020) randomized patients to either SML or threshold conventional laser. Threshold conventional laser was given with 577 nm laser with time 0.05 s, spot size 100 μm and 9-spot matrix with one burn space (Sun et al., 2020). The authors outlined that this treatment is

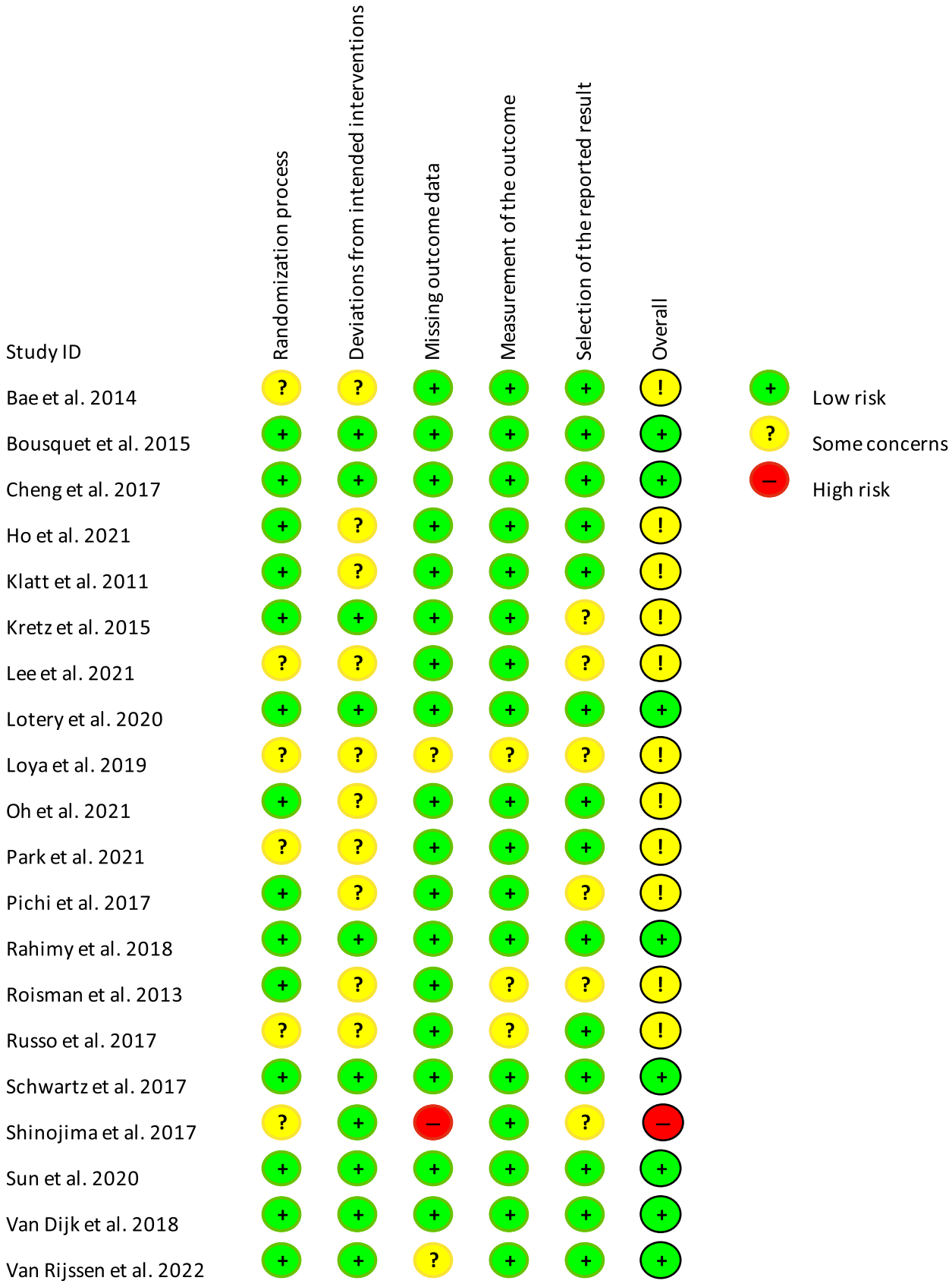

FIGURE 2 Risk of bias of individual studies.

not appropriate for juxta or subfoveal leakage due to the retinal damage, which may lead to central or paracentral scotomas (Sun et al., 2020). Both treatment modalities led to improvements in BCVA, which did not differ significantly between the groups (Sun et al., 2020). The group treated with threshold conventional laser had more patients with complete resolution of the SRF, but this difference was observed as a borderline-significant trend (Sun et al., 2020).

Three studies randomized patients to either SRT or placebo. Klatt et al. (2011) found that SRT was significantly effective for resolution of SRF and improvement

TABLE 1 Characteristics of studies in review

Reference	Country	Definition of chronic CSC	Inclusion criteria	Exclusion criteria
Bae et al. (2014)	South Korea	Chronic CSC with visual disturbance persisting for >6 months or recurrent CSC (defined as the recurrence of SRF and visual symptoms after complete recovery)	• BCVA 0.0–1.0 logMAR • SRF on OCT >3 months • Multifocal/diffuse RPE decompensation with leakage on FA • Choroidal vascular hyperpermeability and abnormal dilation on ICGA	• Previous treatment • CNV or PCV • Any other ocular diseases that can affect BCVA • Significant media opacity • Any intraocular surgery (except uncomplicated cataract surgery >3 months before enrolment) • Systemic steroid or anti-VEGF treatment ≤12 months • Uncontrolled glaucoma with intraocular pressure >21 mmHg despite treatment
Bousquet et al. (2015)	France	Visual symptoms and OCT follow-up consistent with CSC for >3 months of duration with no spontaneous reduction in SRF	• Aged 18–70 years • BCVA 20/200–20/32 Snellen • Fovea involving SRF on OCT • Angiographic leakage caused by CSC on FA • Visual symptoms and OCT follow-up consistent with CSC for >3 months of duration with no spontaneous reduction in SRF	• Previous treatment • CNV, PCV, pseudovitelliform lesions, or other macular abnormalities • Systemic contraindication for spironolactone treatment: liver or kidney failure, or hyperkalaemia • Treatment with NSAID or concomitant drugs that increase potassium level • Allergy to the study drug, lactose, or fluorescein • Pregnancy
Cheng et al. (2017)	Taiwan	Symptomatic CSC of ≥4 months	• BCVA ≥20/400 Snellen • SRF on OCT with persistent or progressive visual symptoms consistent with chronic CSC for >4 months • Active leakage on FA caused by CSC • Abnormal dilated choroidal vasculature with hyperpermeability on ICGA	• Previous interventional treatment for CSC • CNV, PCV, angioid streak, pathological myopia, macular degeneration, any diabetic retinopathy or maculopathy, retinal vein occlusion, uveitis or other retinal diseases • Any intraocular surgery • Systemic corticosteroid usage ≤3 months before the occurrence of clinical symptoms • Systemic contraindication for PDT
Ho et al. (2021)	China	CSC with history >3 months	• History of CSC >3 months	• Prior macular laser or PDT • Use of systemic steroids • Multifocal CSC • Evidence of diffuse retinal pigment epitheliopathy • Patients with fibrin, pigment or PED, which may produce shadow artefacts on OCTA
Klatt et al. (2011)	Germany	CSC with a history of ≥3 months of reduced visual acuity	• Aged ≥18 years • Reduced BCVA >3 months • BCVA ≥20 ETDRS letters • SRF on OCT • Active leakage on FA	• Other retinal diseases or glaucoma • Significant media opacity • Previous PDT or laser coagulation for CSC • Systemic steroid treatment, Cushing's disease, renal diseases, pregnancy or breastfeeding
Kretz et al. (2015)	Germany	Non-resorbing CSC that had been present for >3 months	• Diagnosis of non-resorbing CSC • No more than 2 active leakage sites on FA • SRF for >3 months on OCT	• Use of exogenous corticosteroids (oral, topical, intranasal or intravenous) ≤6 months • Diabetic retinopathy, uveitis, any hereditary retinal/macular disease or any history of intraocular surgery

TABLE 1 (Continued)

Reference	Country	Definition of chronic CSC	Inclusion criteria	Exclusion criteria
Lee et al. (2021)	South Korea	Persistent (≥3 months) SRF involving the fovea	• Aged 19–65 years • SRF ≥3 months on OCT • Focal or diffuse active hyperfluorescent leakages on FA, due to CSC	• BCVA ≤20/200 Snellen • CNV, PCV, or other chorioretinal diseases • Significant media opacity • RPE atrophy >1000 μm in diameter, involving the fovea • Large PED >300 μm in width or 100 μm in height • Any conventional laser photocoagulation or PDT for CSC • Any corticosteroids ≤1 year; spironolactone, acetazolamide, or ketoconazole ≤2 months; intravitreal anti-VEGF ≤10 weeks
Lotery et al. (2020)	United Kingdom	CSC of ≥4 months duration	• Aged 18–60 years • Treatment-naïve CSC of ≥4 months duration	• CNV, or any other disease which could affect BCVA or cause retinal fluid or SRF • Myopia >6 D • Hyperkalaemia
Loya et al. (2019)	Pakistan	Chronic CSC with clinical symptoms >3 months	• CSC with clinical symptoms >3 months • BCVA <0.2 logMAR • CRT on OCT >300 μm	• Acute CSC • History of intravitreal injection or laser photocoagulation • History of trauma or other ocular pathology, systemic illness (diabetes, hepatitis, renal insufficiency, elevated creatinine or abnormal liver function tests) • Use of medication which interacts with rifampicin
Oh et al. (2021)	South Korea	CSC with clinical symptoms >3 months	• Aged 19–55 year • CSC with clinical symptoms >3 months • BCVA ≥20/200 Snellen • SRF involving the fovea • 1–3 active leakage sites in FA	• CNV, PCV, or other retinal diseases • Foveal RPE atrophy with a diameter of ≥1000 μm • Significant media opacity • Any laser or PDT • Any intravitreal anti-VEGF, corticosteroids ≤1 year, intraocular surgery ≤6 months • PED directly related to the point of leakage with a diameter of >1000 μm
Park et al. (2021)	South Korea	CSC with persistent symptoms for ≥4 months	• Persistent symptoms for ≥4 months • SRF with or without serous • PED on OCT • RPE changes or focal leakage on FA • Abnormally dilated choroidal vasculature and active leakage on ICGA corresponding to the area of leakage area on FA • Descending atrophic tracts	• Any previous treatment for CSC • CNV, PCV, or other maculopathies • Exogenous corticosteroid treatment or systemic conditions • Myopia ≥6 D • Any intraocular surgery ≤6 months
Pichi et al. (2017)	Italy	Persistent CSC for ≥3 months with stable SRF	• BCVA 0.1–1.0 logMAR • SRF or CME involving the fovea • Active angiographic leakage on FA • Visual symptoms and OCT compatible with chronic CSC	• Prior treatment with PDT, focal laser • photocoagulation of the RPE, or intravitreal anti-VEGF • CNV, PCV, other macular abnormalities, or myopia ≥6 D • Systemic contraindication to treatment with spironolactone or eplerenone including kidney or liver disease, hyperkalaemia or concomitant medications that increased potassium levels and pregnancy

(Continues)

TABLE 1 (Continued)

Reference	Country	Definition of chronic CSC	Inclusion criteria	Exclusion criteria
Rahimy et al. (2018)	United States	Chronic CSC defined as symptoms and subfoveal fluid persisting >3 months	• Aged ≥18 years • Chronic CSC	• Absence of SRF • Prior anti-VEGF or PDT ≤3 months • Pregnancy or actively trying to conceive
Roisman et al. (2013)	Brazil	CSC persisting >6 months	• CSC persisting >6 months	–
Russo et al. (2017)	Italy	Clinical features and symptoms of CSC ≥3 months	• Aged ≥18 years • BCVA ≥20/200 Snellen • SRF and/or serous PED involving the fovea on OCT, with or without serous PED • Single or multiple active angiographic leakages on FA images caused by CSC and no other disease • Abnormally dilated choroidal vasculature and other features on ICGA consistent with the diagnosis of CSC	• Any previous treatment for CSC • CNV or any other maculopathy
Schwartz et al. (2017)	Israel	Chronic CSC foveal involvement >4 months	• Age 18–65 years • Decreased BCVA due to CSC • OCT finding of chronicity, defined as persistent SRF involving the foveal centre >4 months • Evidence of leakage caused by CSC on FA	• CNV, other macular diseases or uveitis • Diabetic patients with a history of microalbuminuria • Intraocular surgery ≤3 months • Systemic contraindication for eplerenone treatment • Pregnancy, lactating or not using oral contraceptive pills • Allergy to fluorescein • Previous PDT or anti-VEGF if given ≤3 months
Shinojima et al. (2017)	Japan	Chronic CSC defined as symptomatic history of ≥6 months	• SRF on OCT and late-phase hyperfluorescence on FA	• CNV, PCV or other macular diseases on ICGA
Sun et al. (2020)	China	CSC with SRF in macular centre ≤6 months	• Aged ≥18 years • SRF involving macular centre • CRT on OCT ≥250 μm • BCVA ≥64 ETDRS letters • Leakage points on FA are limited to ETDRS ring 2 or 3	• PDT and/or laser treatments in the study eye <3 months • CNV, PCV or AMD
van Dijk et al. (2018)	European Multicentre	Chronic CSC defined as presence of clinical features and symptoms ≥6 weeks	• Aged ≥18 years • SRF and visual symptoms >6 weeks • Presence of active leakage on FA or hyperfluorescence on ICGA	• Any previous CSC treatment • Continuous or progressive vision loss, or both, SRF, or a combination thereof for >18 months • Soft drusen in the study eye, fellow eye or both; any CNV, or intraretinal fluid; myopia >6 D; profound chorioretinal atrophy in the central macular area; non-CSC diagnosis attributable for SRF or vision loss; or BCVA ≤20/200 Snellen • Steroid use (current or ≤3 months, or anticipated start ≤ first 7 to 8 months after the start of the trial) • Contraindications for FA, ICGA or PDT treatment

TABLE 1 (Continued)

Reference	Country	Definition of chronic CSC	Inclusion criteria	Exclusion criteria
van Rijssen et al. (2022)	The Netherlands	Chronic CSC defined as presence of clinical features and symptoms ≥6 weeks	• Aged ≥18 years • Active chronic CSC • SRF and visual symptoms >6 weeks • Foveal SRF on OCT at baseline • ≥1 area of ill-defined hyperfluorescent leakage compatible with chronic CSC • Hyperfluorescent areas on ICGA	• Any previous CSC treatment, or MR antagonist treatment for any reason • Treatment with steroids ≤3 months prior to trial or expected ≤2 years after trial start • Continuous and/or progressive vision loss lasting >18 months or SRF >18 months • Soft drusen in the study eye, fellow eye or both; any CNV, or intraretinal fluid; myopia >6 D; profound chorioretinal atrophy in the central macular area; non-CSC diagnosis attributable for SRF or vision loss; or BCVA ≤20/200 Snellen • Contraindications for FA, ICGA, PDT or eplerenone treatment

Abbreviations: BCVA, best-corrected visual acuity; CME, cystoid macular oedema; CNV, choroidal neovascularization; CRT, central retinal thickness; CSC, central serous chorioretinopathy; D, dioptre; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; ICGA, indocyanine green angiography; logMAR, logarithm of the minimum angle of resolution; MR, mineralocorticoid receptor; NSAID, non-steroid anti-inflammatory drug; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; PED, pigment epithelium detachment; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

in BCVA. Lee et al. (2021) found that SRT treatment with a feedback system was effective and lead to significantly higher improvements in the SRT group in terms of reduction in SRF height and complete resolution of the SRF, but the groups did not differ regarding BCVA at follow-up. Oh et al. (2021) found that SRT treatment with a feedback system led to increased resolution of SRF and better BCVA, but these differences did not reach statistical significance. In a mixed model analysis, the authors demonstrated that the SRT group had statistically significantly more reduction in SRF on OCT (Oh et al., 2021).

3.2.2 | Studies of intravitreal anti-vascular endothelium growth factor (anti-VEGF) injections

One study investigated efficacy of intravitreal anti-VEGF versus low-fluence PDT in cCSC. Bae et al. (2014) randomized patients to either half-fluence PDT or three-monthly intravitreal injections of ranibizumab. At the 3-month follow-up, rescue treatment was performed if SRF persisted on OCT using the non-allocated treatment option (i.e. for the half-fluence PDT group, intravitreal ranibizumab was given; for the intravitreal ranibizumab group, half-fluence PDT was given; Bae et al., 2014). At 3-month follow-up, the half-fluence PDT group showed SRF resolution in 89% of patients, whereas the ranibizumab group had SRF resolution in 31%, and the need for rescue therapy was greater in the ranibizumab group (Bae et al., 2014). The improvement in BCVA was significantly higher in the half-fluence PDT group compared with the ranibizumab group; however, after rescue therapy and at 12-month follow-up, the outcomes were largely similar (Bae et al., 2014).

3.2.3 | Studies of mineralocorticoid receptor antagonists

Six studies investigated efficacy of mineralocorticoid receptor antagonists. Bousquet et al. (2015) randomized 15 eyes to either spironolactone 50 mg daily or placebo. The authors reported that the spironolactone group experienced a statistically significant reduction in subfoveal choroidal thickness and that changes in BCVA did not differ significantly between the groups (Bousquet et al., 2015). Complete resolution of SRF, a key element in CSC, was not reported (Bousquet et al., 2015). Lotery et al. (2020) evaluated oral eplerenone (25 mg daily for 1 week and then 50 mg daily for 1 year) compared with placebo in the multicentre VICI trial. No significant differences between the groups were observed at 3 or 12 months regarding resolution of SRF, improvement in BCVA or in vision-related quality of life measured using the National Eye Institute Vision Function Questionnaire 25-item (Lotery et al., 2020). Pichi et al. (2017) compared 3 groups: (1) spironolactone 25 mg daily for 1 week increased to 50 mg daily for the following 3 weeks and then shifted to eplerenone 50 mg daily for 1 month; (2) eplerenone 25 mg daily for 1 week increased to 50 mg daily for the following 3 weeks and then shifted to spironolactone 50 mg daily for 1 month; (3) placebo

TABLE 2 Characteristics of study groups in studies in review

Reference	Study groups	Age, years	Females, %	BCVA, logMAR	*N* allocated to group	*N* remained throughout study
Bae et al. (2014)	Half-fluence PDT	51 ± 8	17%	0.38 ± 0.24	18 eyes	18 eyes
	Intravitreal ranibizumab	49 ± 8	19%	0.36 ± 0.18	16 eyes	14 eyes
Bousquet et al. (2015)	Oral spironolactone	48 ± 9	13%	0.21 ± 0.22	8 eyes	8 eyes
	Placebo	45 ± 6	29%	0.24 ± 0.19	7 eyes	7 eyes
Cheng et al. (2017)	Half-dose PDT	47 ± 8	15%	0.39 ± 0.28	20 eyes	20 eyes
	Half-fluence PDT	45 ± 8	10%	0.36 ± 0.41	20 eyes	20 eyes
Ho et al. (2021)	SML	53 ± 10	22%	0.31 ± 0.30	18 eyes	18 eyes
	Half-dose PDT	51 ± 11	27%	0.23 ± 0.20	15 eyes	15 eyes
Klatt et al. (2011)	SRT	43 ± 6	0%	0.90 ± 0.23	14 eyes	14 eyes
	Control	45 ± 6	25%	0.87 ± 0.18	16 eyes	16 eyes
Kretz et al. (2015)	SML	47 ± 8	30%	−0.04 ± 0.29	20 eyes	20 eyes
	Half-dose PDT	47 ± 8	17%	0.04 ± 0.23	24 eyes	24 eyes
Lee et al. (2021)	SRT	44 ± 8	23%	0.25 ± 0.22	22 eyes	22 eyes
	Control	47 ± 9	14%	0.20 ± 0.14	22 eyes	20 eyes
Lotery et al. (2020)	Oral eplerenone	47 ± 7	26%	0.16 ± 0.10	57 eyes	54 eyes
	Placebo	50 ± 8	25%	0.14 ± 0.13	57 eyes	51 eyes
Loya et al. (2019)	Oral rifampicin 600 mg for 1 month	–	38%	0.85 ± 0.19	48 eyes	48 eyes
	Oral rifampicin 300 mg for 3 months	–	45%	0.74 ± 0.21	43 eyes	43 eyes
Oh et al. (2021)	SRT	45 ± 7	16%	–	31 eyes	29 eyes
	Placebo	46 ± 7	24%	–	37 eyes	37 eyes
Park et al. (2021)	Low-fluence (50%) PDT	51 ± 7	13%	0.33 ± 0.31	15 eyes	15 eyes
	Low-fluence (40%) PDT	49 ± 10	19%	0.32 ± 0.30	16 eyes	15 eyes
	Low-fluence (30%) PDT	55 ± 10	12%	0.28 ± 0.32	17 eyes	15 eyes
Pichi et al. (2017)	Oral spironolactone	–	–	0.25	20 eyes	20 eyes
	Oral eplerenone	–	–	0.20	20 eyes	20 eyes
	Placebo	–	–	0.25	20 eyes	20 eyes
Rahimy et al. (2018)	Oral eplerenone	50 ± 12	20%	0.39 ± 0.28	Unclear	15 eyes
	Placebo	62 ± 5	20%	0.31 ± 0.09	Unclear	6 eyes
Roisman et al. (2013)	SML	40 ± 6	30%	0.39 ± 0.22	10 eyes	10 eyes
	Placebo	45 ± 4	40%	0.57 ± 0.14	5 eyes	5 eyes
Russo et al. (2017)	Half-dose PDT	43 ± 8	10%	0.36 ± 0.08	20 eyes	20 eyes
	689 nm laser therapy	43 ± 6	15%	0.43 ± 0.07	20 eyes	20 eyes
Schwartz et al. (2017)	Oral eplerenone	51 ± 8	33%	0.60 ± 0.80	13 eyes	13 eyes
	Placebo	47 ± 14	20%	0.20 ± 0.24	7 eyes	6 eyes
Shinojima et al. (2017)	Oral lutein and antioxidants	56 ± 11	14%	0.16 ± 0.27	50 eyes	37 eyes
	Placebo	51 ± 9	14%	0.09 ± 0.24	50 eyes	42 eyes
Sun et al. (2020)	SML	44 ± 9	20%	0.16 ± 0.14	44 eyes	41 eyes
	Threshold conventional laser	45 ± 7	5%	0.14 ± 0.16	44 eyes	43 eyes
van Dijk et al. (2018)	Half-dose PDT	49 ± 9	25%	0.16 ± 0.17	80 eyes	67 eyes
	SML	49 ± 8	14%	0.18 ± 0.18	80 eyes	66 eyes
van Rijssen et al. (2022)	Half-dose PDT	45 ± 10	4%	0.09 ± 0.16	53 eyes	52 eyes
	Oral eplerenone	48 ± 10	9%	0.14 ± 0.26	54 eyes	44 eyes

Note: Continuous data are listed in mean ± standard deviation.

Abbreviations: BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; *N*, number; PDT, photodynamic therapy; SML, subthreshold micropulse laser; SRT, selective retina therapy.

for 4 weeks, and then shifted to spironolactone 50 mg for 1 month. The authors reported statistically significant improvements in BCVA and SRF height in groups 1 and 2 after 1–2 months, but no changes in group 3 at 1-, 2- or 4-month follow-up despite therapy with spironolactone after the first 4 weeks. Rahimy et al. (2018) compared

TABLE 3 Efficacy outcomes and safety events in studies in review

Reference	Study groups	Follow-up eligible for this review	Evaluation of subretinal fluid resolution	Evaluation of change in BCVA	Vision-related quality of life	Safety events
Bae et al. (2014)	Half-fluence PDT	2 months	Yes	Yes	–	None
	Intravitreal ranibizumab					3 in 16 reported ocular pain or conjunctival haemorrhage after injection
Bousquet et al. (2015)	Oral spironolactone	1 month	–	Yes	–	None
	Placebo					None
Cheng et al. (2017)	Half-dose PDT	3 months	Yes	Yes	–	None
	Half-fluence PDT					None
Ho et al. (2021)	SML	3 months	Yes	Yes	–	–
	Half-dose PDT					
Klatt et al. (2011)	SRT	3 months	Yes	Yes	–	None
	Control					None
Kretz et al. (2015)	SML	2 months	Yes	Yes	–	None
	Half-dose PDT					None
Lee et al. (2021)	SRT	6 weeks	Yes	Yes	–	4 in 22 reported temporary conjunctival hyperaemia
	Control					None
Lotery et al. (2020)	Oral eplerenone	3 months	Yes	Yes	[a]	30 in 57 had any adverse events of which 0 were categorized as serious
	Placebo					31 in 57 had any adverse events of which 3 were categorized as serious
Loya et al. (2019)	Oral rifampicin 600 mg for 1 month	3 months	–	Yes	–	–
	Oral rifampicin 300 mg for 3 months					
Oh et al. (2021)	SRT	3 months	Yes	Yes	–	6 in 31 reported dry eye, respiratory disorder or vascular disorder
	Placebo					7 in 37 reported dry eye, respiratory disorder or vascular disorder
Park et al. (2021)	Low-fluence (50%) PDT	3 months	Yes	Yes	–	None
	Low-fluence (40%) PDT					1 in 16 had grade 1 choroidal ischemia
	Low-fluence (30%) PDT					2 in 17 had grade 1 choroidal ischemia
Pichi et al. (2017)	Oral spironolactone	2 months	–	Yes	–	1 in 20 developed gynecomastia
	Oral eplerenone					None
	Placebo					None

(Continues)

TABLE 3 (Continued)

Reference	Study groups	Follow-up eligible for this review	Evaluation of subretinal fluid resolution	Evaluation of change in BCVA	Vision-related quality of life	Safety events
Rahimy et al. (2018)	Oral eplerenone	9 weeks	Yes	Yes	–	1 in 15 reported intermittent dizziness and diarrhoea
	Placebo					None
Roisman et al. (2013)	SML	3 months	Yes	Yes	–	None
	Placebo					None
Russo et al. (2017)	Half-dose PDT	2 months	Yes[b]	Yes	–	6 in 20 reported temporary central shadow
	689 nm laser therapy					9 in 20 reported temporary central shadow
Schwartz et al. (2017)	Oral eplerenone	3 months	Yes	Yes	–	1 in 13 had elevated creatine phosphokinase attributed to exercise and not the treatment intervention
	Placebo					None
Shinojima et al. (2017)	Oral lutein and antioxidants	3 months	Yes	Yes	–	–
	Placebo					
Sun et al. (2020)	SML	3 months	Yes	Yes	–	None
	Threshold conventional laser					1 in 44 developed a secondary choroidal neovascularization
van Dijk et al. (2018)	Half-dose PDT	6–8 weeks	Yes	Yes	No difference in NEI-VFQ-25 at 6–7 weeks after treatment start	10 in 80 reported any adverse events, all considered not related to the treatment
	SML					7 in 80 reported any adverse events, all considered not related to the treatment
van Rijssen et al. (2022)	Half-dose PDT	3 months	Yes	Yes	No difference in NEI-VFQ-25 at 3 months after treatment start	3 in 53 reported any adverse events (dental pain, rib contusion, folliculitis)
	Oral eplerenone					18 in 53 reported any adverse events (headache, dizziness, rash, paraesthesia, stomach complaints, fatigue, vasovagal reaction during FA, general malaise, nipple tenderness, heart palpitations, nausea, eczema, sprained ankle, rhinitis, diarrhoea)

Abbreviations: BCVA, best-corrected visual acuity; FA, fluorescein angiography; NEI-VFQ-25, National Eye Institute Vision Function Questionnaire 25-item; PDT, photodynamic therapy; SML, subthreshold micropulse laser; SRT, selective retina therapy.

[a]No difference in NEI-VFQ-25 at 1 year after treatment start. No data for 1–3 months after treatment start.

[b]The authors described a difference in complete resolution of subretinal fluid at 2 months but did not provide numbers; numbers were only provided for outcomes at >10-month follow-up.

eplerenone 25 mg daily for 1 week increased to 50 mg daily for 8 weeks versus placebo. At 9-week follow-up, the authors found that the eplerenone group had a trend towards better BCVA and a statistically significantly lower SRF height (Rahimy et al., 2018). The eplerenone group had complete resolution of the SRF in 33% of eyes, whereas none experienced complete SRF resolution in the placebo group (Rahimy et al., 2018). Schwartz et al. (2017) evaluated eplerenone 50 mg daily or placebo for 3 months. Both groups experienced a reduction in SRF, and complete SRF resolution was obtained in 23% of eyes in the eplerenone group and in 31% in the placebo group (Schwartz et al., 2017). The placebo group experienced a statistically significant improvement in BCVA, whereas the eplerenone group experienced no significant change (Schwartz et al., 2017). van Rijssen et al. (2022) compared eplerenone 25–50 mg (depending on serum potassium levels) to half-dose PDT in the SPECTRA trial. Complete resolution of SRF was obtained in 78% of patients in the half-dose PDT group and in 17% in the eplerenone group (van Rijssen et al., 2022). No significant differences between the groups were observed for BCVA and vision-related quality of life measured using the National Eye Institute Vision Function Questionnaire 25-item (van Rijssen et al., 2022).

3.2.4 | Studies of other therapies

Two studies investigated efficacy of other types of therapies. Loya et al. (2019) studied the effect of oral rifampicin 600 mg daily for 1 month and compared with a group who received oral rifampicin 300 mg daily for 3 months. The authors found no differences between these two dosages in terms of efficacy (Loya et al., 2019). Shinojima et al. (2017) studied oral antioxidant supplementation and compared this to a placebo group. No differences were found at either 1 or 3 months, but after 6 months the authors reported that the supplementation group had a statistically significant improvement in BCVA and subfoveal retinal detachment height, whereas no significant changes were observed in the placebo group (Shinojima et al., 2017).

3.3 | Risk of bias within studies

Low risk of bias was found in 65% of studies for randomization process, 59% for deviations from intended interventions, 89% for missing outcome data, 76% for measurements of the outcome and 65% for selection of the reported results. Overall, we observed a certain trend towards a source of bias in that some studies deviated from intended interventions as patients underwent rescue therapy when the assigned intervention did not lead to relief of symptoms. Risk of bias evaluation of individual studies are summarized in Figure 3.

3.4 | Meta-analyses of outcomes

Certain assumptions were necessary to strengthen our network meta-analyses. We analysed half-fluence PDT and half-dose PDT as an equivalent group, which is hereafter referred as half-dose PDT. Their equivalence in terms of efficacy and safety was shown by the study of Cheng et al. (2017). Since the 689 nm laser therapy is based on the principle of SML, we included the 689 nm laser therapy group in Russo et al. (2017) as an SML group. Oral spironolactone and oral eplerenone were pooled into a single group of mineralocorticoid receptor antagonists, although spironolactone is presumably much more potent. Pichi et al. (2017) showed minimal differences between the two mineralocorticoid receptor antagonists at 2-month follow-up. Placebo and control (i.e. the patient is aware of being observed and receiving no treatment) were pooled into a single group of non-treatment controls. Taken together, we included the following groups of treatments for our network meta-analyses: half-dose or half-fluence PDT, SML, SRT, mineralocorticoid receptor antagonists, intravitreal ranibizumab, threshold conventional laser therapy, antioxidants (oral lutein and antioxidants) and non-treatment controls. This strategy led to exclusion of certain studies from the quantitative analyses: Cheng et al. (2017) (due to comparison within treatment group, i.e. treatment of half-dose PDT versus half-fluence PDT) and Park et al. (2021) (due to comparison within treatment group, i.e. treatment of low-fluence PDT at 30% vs. 40% vs. 50%). In addition, Loya et al. (2019) were also excluded from the analyses since none of the other studies had a rifampicin treatment group, Loya et al. (2019) did not have another treatment or control study group, and hence, the network did not reach out to this study. In total, 16 studies were eligible for the quantitative analysis.

3.4.1 | Resolution of subretinal fluid at approximately 2-month follow-up

This meta-analysis included 14 of the 17 studies available for quantitative analysis since Bousquet et al. (2015) and Pichi et al. (2017) did not provide data on resolution of SRF, and Russo et al. (2017) described a difference in resolution in SRF at 2 months but did not provide specific numbers. The 14 studies provided a total of 880 eyes allocated to any study group. Data were included in the meta-analysis using an intention-to-treat approach. The network plot illustrates that the treatment groups half-dose PDT, oral mineralocorticoid receptor antagonists, SML and controls are key points in the plot and are study groups to which other therapies are compared (Figure 3). Compared with controls without treatment, efficacy of treatment on the resolution of SRF can be ranked as the following (starting from the least effective to the most effective treatment, *p*-values below 0.05 indicate statistically significant difference from controls without treatment) (Figure 3):

- Intravitreal ranibizumab (OR: 0.8; 95% CI: 0.1 to 7.1; $p = 0.83$).
- Mineralocorticoid receptor antagonists (OR: 1.0; 95% CI: 0.4 to 2.4; $p = 0.99$).
- Antioxidants (OR: 1.9; 95% CI: 0.5 to 6.9; $p = 0.35$).
- SRT (OR: 3.4; 95% CI: 1.7 to 6.8; $p = 0.00075$).
- SML (OR: 13.5; 95% CI: 0.9 to 207.6; $p = 0.062$).

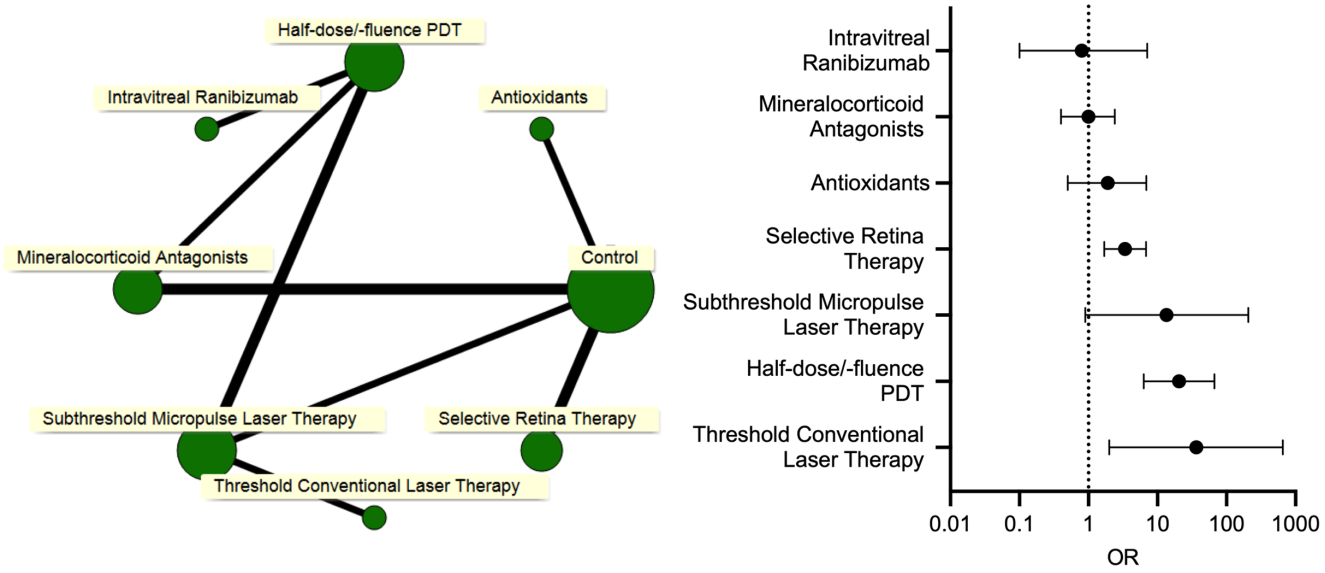

FIGURE 3 Network meta-analysis of the treatment efficacy on complete resolution of subretinal fluid at ~2-month follow-up. *Left*: Network plot which illustrates comparisons in the meta-analysis. Size of the green dots illustrates the number of studies including that specific treatment/control group. *Right*: Summary estimates (dots and whiskers) for each type of intervention are provided as odds ratio (OR) compared with the likelihood of complete resolution of subretinal fluid in the control group at ~2-month follow-up (dotted line at OR = 1). Treatment groups are listed according to their ranking, that is intravitreal ranibizumab is the least effective treatment, and conventional laser therapy is the most effective treatment. Treatment does not yield statistically significant different outcome compared with control when the confidence interval includes the dotted line.

- Half-dose PDT (OR: 20.6; 95% CI: 6.3 to 66.7; $p < 0.0001$).
- Threshold conventional laser therapy (OR: 36.4; 95% CI: 2.0 to 655.7; $p = 0.015$).

3.4.2 | Change in best-corrected visual acuity at approximately 2-month follow-up

This meta-analysis included all the 17 studies available for quantitative analysis. The network plot illustrates that the treatment groups half-dose PDT, oral mineralocorticoid receptor antagonists, SML, and controls are key points in the plot and are study groups to which other therapies are compared (Figure 4). Compared with controls without treatment, efficacy of treatment on the change in BCVA (logMAR) can be ranked as the following (starting from the least effective to the most effective treatment, *p*-values below 0.05 indicate statistically significant difference from controls without treatment) (Figure 4):

- Intravitreal ranibizumab (WMD: +0.02 logMAR; 95% CI: −0.12 to +0.15 logMAR; $p = 0.82$).
- Antioxidants (WMD: −0.01 logMAR; 95% CI: −0.06 to +0.04 logMAR; $p = 0.72$).
- SRT (WMD: −0.03 logMAR; 95% CI: −0.09 to +0.03 logMAR; $p = 0.27$).
- Mineralocorticoid receptor antagonists (WMD: −0.05 logMAR; 95% CI: −0.10 to +0.01 logMAR; $p = 0.099$).
- Half-dose PDT (WMD: −0.13 logMAR; 95% CI: −0.20 to −0.06 logMAR; $p = 0.00021$).
- SML (WMD: −0.16 logMAR; 95% CI: −0.29 to −0.03 logMAR; $p = 0.013$).
- Threshold conventional laser therapy (WMD: −0.17 logMAR; 95% CI: −0.31 to −0.03 logMAR; $p = 0.019$). (Figure 5)

Our sensitivity analyses with different assumptions on the correlation coefficient showed similar direction of results; however, the statistical significance of improvements in BCVA were lost for the threshold conventional laser therapy and SML treatments, with only half-dose PDT remaining as a treatment with a statistically significant BCVA improvement, in the assumption of a correlation coefficient *C* of 0.5 (i.e. moderate correlation between BCVA numbers before and after treatment) (Figure 5). Exact details of the results of the sensitivity analyses are provided in Appendix S3.

3.5 | Vision-related quality of life and safety-related events

Vision-related quality of life was only reported in Lotery et al. (2020), Van Dijk et al. (2018) and van Rijssen et al. (2022). All used the National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) to evaluate this aspect. In the comparison between half-dose PDT versus SML, no difference was observed in NEI-VFQ-25 at 6–7 weeks (van Dijk et al. 2018). In the comparison between half-dose PDT and oral eplerenone, no difference was observed in NEI-VFQ-25 at 3 months (van Rijssen et al., 2022). In the comparison between oral eplerenone and placebo, Lotery et al. (2020) only provided data for NEI-VFQ-25 at 12 months and here no significant difference was observed between the groups (Lotery et al., 2020). Because of the limited amount of data, quantitative analyses were not conducted. Study results are summarized in Table 3.

Safety/adverse events were reported in 17 studies. Of these, 5 studies reported no events. Remaining events reported were predominantly all mild in nature, heterogeneous in reporting and did not allow for quantitative

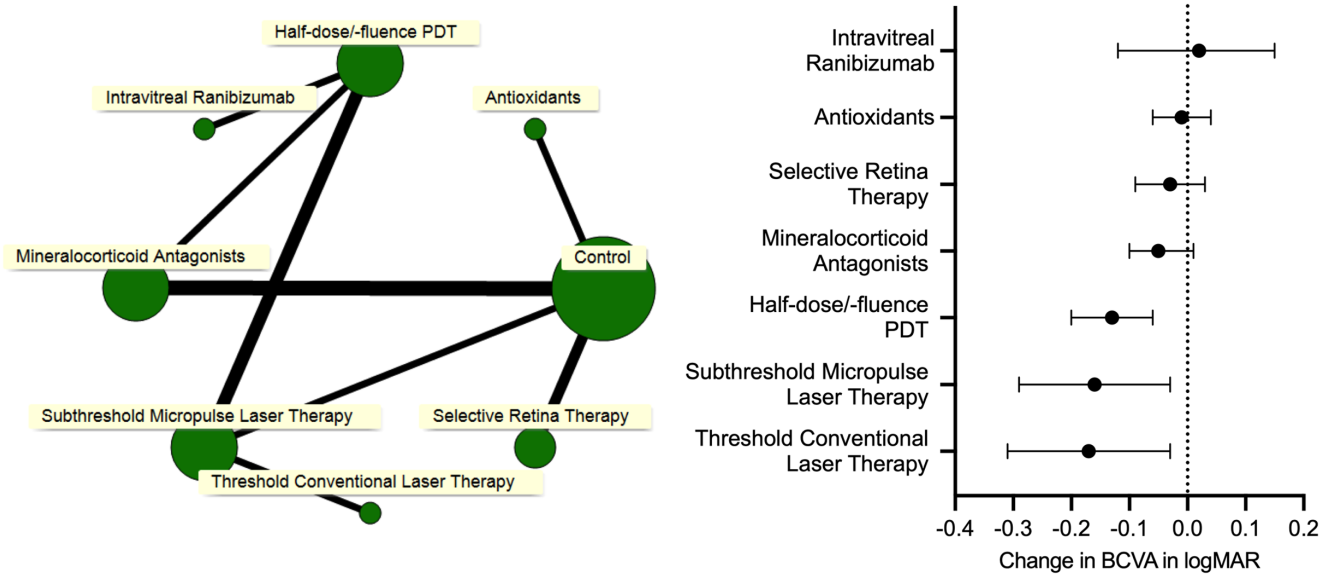

FIGURE 4 Network meta-analysis of the treatment efficacy on the change in best-corrected visual acuity (BCVA) in logMAR at ~2-month follow-up. *Left*: Network plot which illustrates comparisons in the meta-analysis. Size of the green dots illustrates the number of studies including that specific treatment/control group. *Right*: Summary estimates (dots and whiskers) for each type of intervention are provided as weighted mean difference in change in BCVA in logMAR compared with that of the control group at ~2-month follow-up (dotted line at change in BCVA at 0.0 logMAR). Treatment groups are listed according to their ranking, that is antioxidants are the least effective treatment, and conventional laser therapy is the most effective treatment. Treatment does not yield statistically significant different outcome compared with control when the confidence interval includes the dotted line.

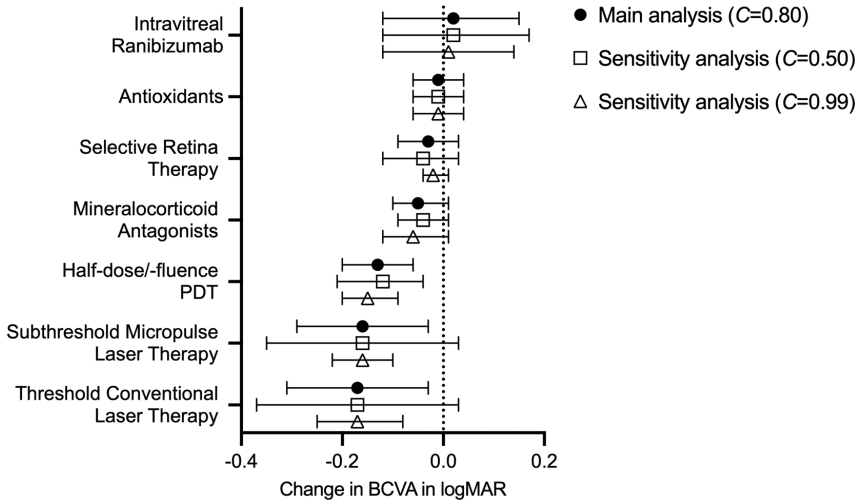

FIGURE 5 Summary estimates (dots and whiskers) for each type of intervention are provided as weighted mean difference in change in best-corrected visual acuity (BCVA) in logMAR compared to that of the control group at ~2 months follow-up (dotted line at change in BCVA at 0.0 logMAR). This figure includes both the results of the main analysis as well as the results of the sensitivity analysis performed under the different assumptions of the correlation coefficient C that is the correlation between BCVA values before and after treatment.

analyses. All safety-related events are summarized for specific treatment groups in individual studies in Table 3.

4 | DISCUSSION

Based on this systematic review and network meta-analysis including a total of 1172 eyes with cCSC, we conclude that half-dose or half-fluence PDT, threshold conventional laser therapy, and to a much lesser degree SRT, appear to perform significantly better than controls for short-term complete resolution of SRF. Only half-dose or half-fluence PDT provided a significantly better short-term improvement in BCVA compared with controls. The superiority of half-dose or half-fluence PDT over other treatments for cCSC in terms of BCVA improvement is less relevant, as cCSC patients often have a relatively good baseline BCVA and a ceiling effect in measurements limits the measurable change in BCVA. Taken together, for practical purposes, there seem to be three treatment modalities with significant impact on cCSC, that is on the anatomical feature of SRF resolution, which if left untreated may lead to permanent retinal damage. All three treatment types have certain specific shortcomings to be considered.

Conventional/suprathreshold laser therapy has been used for CSC for several decades (Leaver &

Williams, 1979; Novak et al., 1987), and reports have been published on the experience with different types of lasers (van Rijssen et al., 2019). The aim of this type of treatment is to close the defect in the RPE by applying photocoagulation in the area of leakage. Our network meta-analysis finds statistically significant and high OR for complete SRF resolution by this treatment modality, which is also in line with recent retrospective cohort studies of patients treated with conventional laser photocoagulation (Chhablani et al., 2014; Zhou et al., 2022). However, as application of conventional laser photocoagulation in the fovea leads to vision loss, central scotoma and risk of foveal neovascularization, this treatment may only be relevant for the minority of cCSC cases with extrafoveal leakage points, where access to PDT may be limited, and where costs related to treatment may be a factor in treatment decision.

Selective retina therapy is a treatment modality which is currently still considered experimental. It is based on micropulse laser technology; however, unlike micropulse laser—which does not cause any retinal tissue damage (but has also not been shown to be effective in RCTs in cCSC)—SRT has been hypothesized to induce selective RPE damage without affecting the overlying photoreceptors (Lee et al., 2021; Oh et al., 2021). At present, a clear treatment strategy or proven effective settings remains to be elucidated, complicating a comprehensive SRT strategy in CSC and other diseases. In our systematic review and meta-analysis, this treatment modality performed better than controls on the resolution of SRF, although the OR of 3.4 was at an order of magnitude lower than that of both half-dose or half-fluence PDT (OR: 20.6) and threshold conventional laser therapy (OR: 36.4). Adverse events did not differ between those receiving SRT and placebo (Lee et al., 2021; Oh et al., 2021). However, the evidence base and practical clinical experience around the globe with this technology is currently limited and treatment outcomes should therefore be interpreted with caution.

Half-dose or half-fluence PDT seems to be the only viable treatment modality for patients with cCSC. Half-dose or half-fluence PDT has been shown to be safe in both acute CSC and cCSC (van Rijssen et al., 2019). Hence, half-dose or half-fluence PDT is widely considered the first-line and preferred therapy of cCSC (van Dijk et al., 2020), also because of a treatment efficacy that is equivalent to PDT with standard settings (Sirks et al., 2022; van Rijssen et al., 2019). Considering that the disease has pathophysiological origins in the choroid, with pachyvessels as result of venous congestion and increased hydrostatic pressure from the choroid towards the retina, it makes great mechanistically sense that PDT is strongly effective not only on the short-term but also for reducing the risk of recurrence and preservation of long-term visual function (van Rijssen, van Dijk, et al., 2021; Vasconcelos et al., 2013). Maruko et al. (2010) investigated subfoveal choroidal thickness after treatment with half-dose PDT and compared to treatment with conventional laser photocoagulation. While conventional laser photocoagulation treatment was not associated with any significant change in subfoveal choroidal thickness, half-dose PDT led to a significant increase in subfoveal thickness in the first few days after treatment, whereafter the subfoveal choroidal thickness decreased to levels significantly below baseline, towards more normal levels, after 1 week and further after 4 weeks (Maruko et al., 2010). van Rijssen, Hahn, et al. (2021) evaluated ICGA after treatment of cCSC with either half-dose PDT or SML. Half-dose PDT led to decreased areas of hyperfluorescence, whereas no significant changes were observed after SML treatment (van Rijssen, Hahn, et al., 2021). These areas of hyperfluorescence correspond to choroidal vascular hyperpermeability and illustrate the ability of PDT to remodel the choroid and presumably alleviate the hydrostatic pressure from the choroid towards the retina. Indeed, this exact consequence of half-dose PDT was investigated by Feenstra et al. (2022), who found that half-dose PDT was superior to SML in terms of reduction in RPE detachments in cCSC. The reduction in macular RPE detachments may reflect that the hydrostatic pressure from the choroid towards the retina is markedly reduced, facilitating SRF resolution through a reconstitution of a more normal equilibrium of the micro-environment of the neuroretina, RPE and choroid. Considering these PDT-induced effects on the choroid, it is unsurprising that the favourable short-term effects of PDT for cCSC seem to be sustained with favourable long-term efficacies, with prolonged SRF resolution and reduction in the risk of SRF recurrence, at up to 4 years of follow-up (van Rijssen, van Dijk, et al., 2021; Vasconcelos et al., 2013). Unfortunately, there is a worldwide shortage of verteporfin at the time of writing (Sirks et al., 2022), which is the photosensitive agent administered intravenously before PDT can be performed, and therefore, a main shortcoming of the PDT strategy is currently the limited access to treatment. However, the production of verteporfin has been resumed recently, and it is expected that the medication shortage will be solved later in 2022.

Several limitations of the current study are important to consider when interpreting its results. First, we distinguished between acute and cCSC, whereas the actual definition and classification of CSC remain a subject of continuing debate that still deserves attention (Chhablani et al., 2020, 2022; van Rijssen et al., 2019). Second, retinal sensitivity measured using microperimetry may be a more sensitive evaluation of visual outcome than the BCVA that is highly prone to the ceiling effect in cases of CSC. Examples of microperimetry utilization in the evaluation of cCSC treatment efficacy can be found in the PLACE trial and SPECTRA trial, which found a significant improvement of retinal sensitivity after half-dose PDT (van Dijk et al., 2018; van Rijssen et al., 2022). Long-term significant benefit of half-dose PDT measured using microperimetry has also been reported in a cohort study (Iwase et al., 2020). Microperimetry remains underutilized in RCTs of cCSC and was not considered as an outcome for this study due to the lack of meta-analytic potential. Third, our analyses do not consider any potential differences in treatment efficacy between different ethnicities, which may be a point that deserves more attention. Finally, our conclusions are only as good as the studies from which we extracted data, which is of course a limitation of any

systematic review. For network meta-analyses in particular, there may be biases related to specific areas within the network. In particular, we observed that studies of mineralocorticoid receptor antagonists had more strict eligibility criteria for participants, that is biochemical screening was made to exclude patients with systemic contraindications to avoid hyperkalaemia or any other mineralocorticoid receptor antagonist-related potential adverse effect (Table 1). However, it is our speculation that this bias may only provide little if any influence on the results of our analyses.

Moreover, it should be stressed that outcomes of this review are focused on short-term efficacies, which we believe is an important clinical question for evaluation and decision-making. Long-term efficacy results also deserve attention as considerations need to be made in terms of ensuring long-term visual function and reducing the risk of recurrence. Meta-analyses on long-term data are challenged by the fact that many studies only report short-term outcomes. However, few large RCTs provide insight into long-term follow-up on efficacy and safety of different treatment modalities. The VICI trial found that oral eplerenone treatment was not superior to placebo for cCSC at 12 months (Lotery et al., 2020). The PLACE trial found that half-dose PDT was superior to SML at long-term follow-up at up to 9 months after treatment (van Dijk et al., 2018), and in the SPECTRA trial half-dose PDT was superior to oral eplerenone treatment at 1-year follow-up (van Rijssen et al., 2022). In a prospective follow-up study of 54 participants of the PLACE trial, at 20 months after treatment, cCSC patients successfully treated with half-dose PDT were less likely to have recurrences of SRF compared with those successfully treated with SML (van Rijssen, van Dijk, et al., 2021). These reports collectively suggest that short-term significant treatment effect of half-dose PDT is likely to sustain on long-term and significantly reduces the risk of recurrence, which underscore the notion that half-dose PDT seems to be the best treatment option available today for cCSC patients (van Rijssen et al., 2019).

Taken together, treatment of cCSC is still a challenging topic. We confirm that half-dose or half-fluence PDT is efficacious in complete resolution of SRF. When PDT is unavailable, select cases with extrafoveal leakage points may benefit of conventional laser therapy, at least on short-term. Shortage issues with verteporfin should not lead to employment of treatment modalities that have been found not to be efficacious. Patients with cCSC can expect neither significant improvement in functional nor anatomical outcome measures by treatments such as mineralocorticoid receptor antagonists or intravitreal anti-VEGF injections, but are instead being put at risk of rare but serious complications. Treatment with anti-VEGF injections is a viable and effective treatment option in CSC cases complicated by macular neovascularization (Chhablani et al., 2015; Smretschnig et al., 2016), and in clinical pictures of macular neovascularization with serous SRF that simulate CSC (Elfandi et al., 2021; Gharehbagh et al., 2018; Petri et al., 2020; van Dijk & Boon, 2021). Future guidelines on the treatment of cCSC need to consider results from our study, which allow comparison of all treatment modalities to non-treatment controls to fully understand how emerging treatment modalities actually perform. This is important as the natural course of the disease exhibits waxing and waning, and therefore, a subset of participants included in any study should be expected to improve over time (Lotery et al., 2020; van Rijssen et al., 2020).

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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