Changes of visual fields in treatment of proliferative diabetic retinopathy
a systematic review
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Title:
Changes of visual fields in treatment of proliferative diabetic retinopathy: a systematic review.

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Abstract

**Purpose:** The aim of this systematic review was to compare certain side effects (visual fields (VF), dark adaptation, colour vision (CV), contrast sensitivity (CS)) of conventional PRP with those of other treatments in PDR.

**Methods:** A systematic literature search was conducted on November 30th, 2018 in PubMed and Embase. The search comprised the key words “proliferative diabetic retinopathy”, “laser”, “treatment” and “anti-vegf”. We included prospective studies and randomized controlled trials that investigated certain side effects (VF, dark adaptation, CV, CS) in treatment of PDR (primary outcome).

**Results:** In total, 1867 articles were screened, and ten studies were included (2176 eyes of 2086 patients examined in the VF studies and 1360 eyes of 1360 patients examined in the CV and CS studies). VF were investigated in ten studies, CV in one study and CS in one study. Treatment modalities included conventional PRP, other modalities of laser treatment and vascular endothelial growth factor (VEGF) inhibitors. Four studies demonstrated a worse VF-impact of PRP than VEGF inhibitors. Seven studies reported of an overall worsening in VF after laser with no differences between different laser approaches. No differences were found in CV or CS.

**Conclusions:** Overall, we found a trend, confirmed in four large studies, towards VEGF inhibitors causing less harm to VF compared to conventional PRP. While, VF was generally depressed after laser, it did not differ between different treatment approaches. Furthermore, it was not possible to make certain conclusions of CV or CS, with only one study in each field.

**Key words:** Proliferative diabetic retinopathy, panretinal photocoagulation, side effects, laser treatment, visual fields, anti-vegf
Introduction

Diabetes mellitus (DM) is one of the largest global health issues which affects around 436 million people in the world (Federation 2019). Diabetic retinopathy (DR) is a well-known long-term complication of DM and a feared cause of blindness (Eden & Klein 2007; Grauslund et al. 2009). The prevalence of DR is approximately 35% and 7% of proliferative diabetic retinopathy (PDR) (Yau et al. 2012), and in a span of 25 years 42% of patients with type 1 diabetes will develop PDR (Grauslund et al. 2009). PDR is principally caused by retinal hypoxia (Stefansson 2006). This induces the upregulation of intraocular vascular endothelial growth factor (VEGF) (Stefansson 2006), which leads to retinal vascular proliferation. These are fragile and introduce a high risk of vitreous haemorrhages or tractional retinal detachment, which can culminate in permanent visual loss.

In 1976, it was found that in patients with PDR, full-scatter retinal laser treatment (panretinal photocoagulation, PRP) can reduce the risk of severe vision loss by 50% (Early Treatment Diabetic Study Research Group 1976). PRP is indicated when high-risk PDR is present (Early Treatment Diabetic Study Research Group 1991) but treatment is often already performed at earlier stages of PDR to avoid the development to high-risk PDR and the complications that follows this disease stage. The proposed mechanism behind PRP is that it reduces the retinal oxygen demand, which decreases VEGF and reverses the proliferation. However, for the last 40 years the technique for PRP has not changed substantially and most patients basically receive the same standard treatment (Early Treatment Diabetic Study Research Group 1981; Early Treatment Diabetic Study Research Group 1991). With this one size fits all approach, a substantial number of patients will either be over- or undertreated. Insufficient treatment may lead to visual loss due to disease progression (Bandello et al. 2001). On the contrary, excessive treatment may cause side effects like loss of visual fields (Blankenship 1987; Pahor 1998; Fong et al. 2007; Boynton et al. 2015), reduced night vision (Pender et al. 1981), and diabetic macular oedema (DMO) (Ferris et al. 1987).

In DR, VEGF-inhibition is already a well-documented treatment of DMO (Diabetic Retinopathy Clinical Research Network 2012), and it has recently been demonstrated that VEGF-inhibition is likely to match the efficacy of PRP in PDR (Sivaprasad et al. 2017; Gross et al. 2018). If this is the case, it would be important to evaluate the side effects of the different treatment options in order to obtain the optimal balance between pros and cons in PDR-treatment. To our knowledge, an
overview with a comparison of the side effects of the different treatments of PDR has not yet been conducted. The aim of this systematic review was to compare certain side effects (visual fields (VF), dark adaptation, colour vision (CV), contrast sensitivity (CS)) of conventional PRP with those of other treatments in PDR.

Methods
The protocol of this systematic review was registered at https://www.crd.york.ac.uk/prospero/ with protocol number: PROSPERO 2018 CRD42018080439. We limited our outcome from the original protocol for specific outcomes (certain side effects) throughout the process of formulating the systematic review to specify the aim and make it more focused.

Eligibility criteria
Study design
We included prospective studies and randomized controlled trials (RCTs).

Participants
We included studies examining human. No restrictions regarding degree of PDR, age, sex or type of diabetes was applied.

Interventions
Conventional PRP defined as an intervention in which the whole periphery of the retina is treated. Xenon, argon, pascal and NAVILAS lasers will be included. We excluded studies that did not have PRP as one of the treatment groups, e.g. studies that evaluated PRP treatment in combination with VEGF inhibitors. We also excluded studies with only one treatment evaluating side effects and studies where none of the treatments were conventional PRP.

Comparators
Types of treatment for PDR other than full PRP (e.g. anti-VEGF, other approaches to PRP, other pharmacological treatments, etc.) and specific associated side effects (VF, DA, CV and CS).

Timing
No restrictions regarding follow-up time or number of participants were applied.

Setting
No restrictions regarding setting was applied.

Language

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We included articles reported in English.

Thus, a systematic search based on PICO (population, intervention, comparison and outcome) was performed (Schardt et al. 2007). In prospective studies of patients with PDR (population) treated with conventional PRP (intervention) and other treatment modalities (comparison) we studied treatment-induced side effects (outcome).

Information sources
PubMed and EMBASE searches were performed on November 30, 2018 (Figure 1). Reference lists of studies included after full-text screening was manually searched for additional studies.

Search strategy
The search and screening of the articles were performed by one reviewer (ASV). Full text screening was performed by two reviewers (ASV + JG). When a disagreement occurred between reviewers, the relevant article was discussed between the reviewers and a common conclusion was reached on whether to include them or not. The Covidence software (Veritas Health Innovation Ltd, Melbourne, Australia) was used in the screening process.

PubMed
All available fields were included, and the search string used was: proliferative diabetic retinopathy AND ((laser) OR (treatment) OR (anti-vegf)); n=3453 results obtained. ‘English’ languages filter used; n=3028 results obtained. To limit the search to Randomized Controlled Trials, Prospective studies, and studies performed on humans a specific search string was used (see appendix 1); n=1028 results obtained.

Embase
Search string used was: proliferative diabetic retinopathy AND ((laser) OR (treatment) OR (anti-vegf)); n=2868 results obtained. The search was limited to ‘English language and article’ and ‘human’; n=1447 results obtained.
The searches resulted in 2475 articles. After 608 duplicates were removed, the remaining 1867 articles were imported into Covidence which were used for data management.

Selection process

The 1867 articles were screened based on titles and discarded if the title did not refer to either side effects (VF, DA, CV and CS) or treatment of PDR. This screening concluded in 311 articles which were included for abstract screening. We only included either prospective studies or randomized controlled trials if they were comparing standard (conventional) PRP laser with any other treatment for PDR. There were no limitations on study size in regard to number of patients or eyes included.

This resulted in 35 articles for full text screening, of which ten fulfilled the inclusion criteria and where included in the systematic review (Figure 1).

Data collection process

Data was extracted independently by meticulously reading through each article and plotting into Review Manager. Data extracted included study design, diabetes type, side effects, number of included eyes, intervention, side effects, follow up time and results. Data was then plotted into a ‘Summary of findings’ table.

Outcomes

Specific side effects; VF, DA, CV and CS.

Risk of bias

Risk of bias was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias (The Cochrane Collaboration 2011). Review Manager 5.3 was used for data management of bias assessment.

Results

Reported outcomes were visual fields (VF) (n=10, (Jampol et al. 2019); (Gross et al. 2015; Gross et al. 2018); (Sivaprasad et al. 2017); (Nagpal et al. 2010); (Buckley et al. 1992); (Muqit et al. 2010);
(Muqit et al. 2013); (Pahor 1998); (ETDRS group (Early Treatment Diabetic Study Research Group 1991)), CS (n=1, (Sivaprasad et al. 2017)) and CS (n=1 (ETDRS group (1991))). A total of 2176 eyes of 2086 patients were examined in the VF studies. A total of 1360 eyes of 1360 patients were examined in the CV and CS studies.

**Visual fields**

Characteristics of the studies investigating VF can be found in Table 1:

_Jampol et al. (2017)_ studied the changes in VF in patients with severe NPDR and PDR receiving either conventional PRP or ranibizumab. A total of 146 patients with NPDR and PDR were included; 69 eyes in the PRP group and 77 eyes in the ranibizumab group. The patients were examined at baseline, 1 and 2 years. Humphrey 30-2 and 60-4 VF were measured (decibel (dB)) at baseline and at first and second year. The 60-4 VF test showed a statistically significant worsening in the PRP group compared to the ranibizumab group at 2 years (-1.4 ± 2.0 dB vs. -0.4 ± 1.9 dB, p<0.001). The article did not provide information about the 30-2 VF, only in relation to changes in retinal nerve fibre layer.

_Gross et al. (2015 and 2018) (DRCR.net Protocol S) studied the changes in VF in patients with severe NPDR and PDR receiving either conventional PRP or ranibizumab. A total of 394 patients with mild NPDR to PDR were included; 203 eyes in the PRP group and 191 eyes in the ranibizumab group. The patients were examined at baseline and every sixteen weeks until 2 years, then again at 3, 4 and 5 years. 30-2 and 60-4 Humphrey VF were measured (in dB) at baseline and every year until year 5. At year 2, 60 eyes (70%) in the ranibizumab group completed the 30-2 VF and 60 (71%) the 60-4 VF. In the PRP group 60 (64%) completed the 30-2 VF and 60 (65%) the 60-4 VF. Both the 60-4 and 30-2 mean score (dB) VF showed a statistically significant worsening in the cumulative mean score change in the PRP group compared to the ranibizumab group at 2 years compared to baseline (60-4 VF: -261±280 dB vs. -29±209 dB, p<0.001, 30-2 VF: -146±311 dB vs 9±209 dB, p=0.001). At year 5, 41 eyes (48%) in the ranibizumab group and 38 (41%) in the PRP group completed both 30-2 and 60-4 VF. While the cumulative mean score in 30-2 VF did not differ between groups (-
190±333 dB vs. -157±334 dB, p=0.64) the cumulative mean score (dB) in 60-4 VF showed a statistically significant worsening in the PRP group compared to the ranibizumab group at 5 years compared to baseline (-348±367 dB vs -199±349 dB, p=0.03).

Sivaprasad et al. (2017) (CLARITY study) examined the changes in VF and CS scores in patients with PDR receiving either conventional PRP or aflibercept. A total of 210 eyes with PDR were included; 104 eyes in the aflibercept group and 106 eyes in the PRP group. The patients were examined at baseline, every four weeks in the aflibercept group and every 8 weeks in the PRP group. Binocular and uniocular Estermann scores (missed spots) were measured at baseline and 52 weeks. The binocular Estermann score of VF showed a statistically significant worse outcome in the PRP group compared to the aflibercept group at 52 weeks (3.2±0.8 missed spots vs. 0.2±0.8 missed spots, p=0.007). Uniocular Estermann score of VF did not did not differ between the two groups at 52 weeks (PRP: 3.9±0.9 missed spots vs. aflibercept: 1.9±0.8 missed spots, p=0.12).

Buckley et al. (1992) investigated the effect of argon (conventional) vs. diode laser on VF in patients with PDR. Forty-six patients with 46 eyes were included; fifteen with PDR receiving PRP, 24 healthy controls, seven patients with diabetes not treated with PRP. The patients were examined and had Humphrey full field (40 degrees superiorly, 55 degrees inferiorly, 45 degrees nasally, 75 degrees nasally) VF performed at baseline and 6 weeks after PRP treatment. The fifteen patients receiving PRP got both argon and diode PRP applied to different parts of the same eye (divided into upper and lower retina) and was used as their own control. VF loss did not differ between the two treatments (absolute loss argon vs. diode; 9.0% vs. 10.8%, p=0.663, threshold loss argon vs. diode; 17.3% vs. 18.7%, p=0.862, absolute loss upper vs. lower; 10.1% vs. 10.5%, p=0.934, threshold loss upper vs. lower; 18.1% vs. 20.0%, p=0.817).

Muqit et al. (2010) investigated the effect of pascal multi-spot PRP given in a single session (SS-PRP) vs. (conventional) single-spot multiple-session PRP (MS-PRP) on VF in patients with PDR. Forty eyes of 40 patients were included in the study; 20 eyes received SS-PRP and 20 eyes received MS-PRP (three sessions across four weeks). The patients were examined at baseline, four, and twelve weeks after PRP. In the SS-PRP group, 24-2 SITA standard Humphrey VF mean deviation
(dB) was statistically significant higher at four weeks (-5.94±2.9 dB vs. -5.21 dB, p<0.05) but not statistically significantly higher, at twelve weeks (-5.94±2.9 dB vs. -5.54 dB, p=0.36). In the MS-PRP group there were no statistically significant changes in mean deviation after PRP (4 weeks: -4.62±3.5 dB vs. -4.23 dB, p=0.58; 12 weeks: -4.62±3.5 dB vs. -5.04 dB, p=0.24). There were no statistically significant differences between the two groups. Regarding to Esterman VF a single patient failed the driving VF post MS-PRP.

*Muqit et al. (2013) (PETER PAN study)* studied the effects of high density 20-ms pascal-targeted retinal photocoagulation (TRP) and reduced fluence/minimally traumatic PRP (MT-PRP) vs. (conventional) standard-intensity PRP (SI-PRP) on VF in patients with PDR. Thirty eyes were included in the study; ten eyes received TRP, ten eyes received MT-PRP and ten eyes received SI-PRP. The patients were examined at baseline, four and twelve weeks after PRP. In the TRP group there was a statistically significant increase in mean deviation (dB) measured by 24-2 SITA standard Humphrey VF at four weeks (+1.17±1.0 dB; 95% CI -0.45 to -1.88, p=0.005) but not at twelve weeks (+0.70±1.0 dB; 95% CI 0.07 to 1.48, p=0.07). In the MT-PRP group there was a statistically significant increase in mean deviation at four weeks (+0.64±0.7 dB; 95% CI 0.12 to 1.15, p=0.02) and at twelve weeks (+0.88±0.9 dB; 95% CI 0.22 to 1.55, p=0.015). In the SI-PRP group there was also a statistically significant increase in mean deviation at four weeks (+1.0±1.0 dB; 95% CI 0.34 to 1.74, p=0.009) and at twelve weeks (+1.0±0.9 dB; 95% CI 0.19 to 1.74, p=0.02). However, there were no statistically significant differences between the three groups.

*Nagpal et al. (2010)* compared the effect of PRP with a conventional 532-nm solid-state green laser (GLX) vs. a 532-nm pattern scan laser (PASCAL) on VF in patients with bilaterally symmetrical PDR. Hundred-twenty eyes of 60 patients were included; 60 eyes receiving GLX and 60 eyes receiving PASCAL. The patients were examined at baseline, months 1, 3 and 6. Humphrey central 30-2 VF was divided into zone A (central 15°) and zone B (15° to 30°) and measured at 1-month follow up on 54 patients. VF did not differ between the two groups in either zone A (p=0.26) or zone B (p=0.09).
Pahor et al. (1998) examined the effect of conventional full- and mild-scatter PRP on central (30°) and peripheral (60°) VF in patients with pre-proliferative DR or PDR. Forty eyes of 32 patients were included; 21 received full-scatter PRP (1200-1600 burns) and 19 received mild-scatter PRP (400-600 burns). The patients were examined at baseline and one month after PRP. Humphrey central VF MD (dB) was statistically significant lower one month after both full- and mild-scatter PRP (full: -4.84±2.65 dB vs. -7.61±4.16 dB, p<0.05; mild: -3.73±2.62 dB vs. -5.21±2.81 dB, p<0.05), but no differences between the groups were found. Peripheral VF did not change after PRP in either groups.

ETDRS group (1991) compared the effect of conventional full- or mild-scatter PRP on VF in patients with moderate-to-severe non-proliferative DR or PDR. The patients had their VF measured at baseline, at four months and at 4 years. 538 eyes received immediate full-scatter PRP and 590 eyes received immediate mild-scatter PRP. The group receiving mild-scatter PRP had a statistically significantly lower loss of Goldmann I/4 VF compared to the full-scatter PRP group (p<0.001) at four months. At 4 years scores for I/4 VF worsened in both groups (p<0.001), but no difference between the two groups was found.

To sum up; ten studies examined the effect of different treatments of PDR on VF. Three studies found that there were a statistically significant worsening in VF (both Humphreys 30-2 and 60-4, and binocular Estermann) in the PRP groups compared to the VEGF inhibitor groups ((Jampol et al. 2019);(Gross et al. 2015); (Sivaprasad et al. 2017)). One study found that this difference between groups were persistent in 60-4 VF after five years, but with a huge drop out rate amongst patients (Gross et al. 2018). Six studies compared different lasers (PASCAL (pattern scan laser), Argon and Diode) and the effect of different approaches to laser on VF and mostly found a loss of VF, but no differences between the treatments ((Buckley et al. 1992); (Nagpal et al. 2010) (Muqit et al. 2010); (Muqit et al. 2013)). Two studies compared full-scatter vs. mild-scatter PRP and found that both treatments caused a worsening of VF after treatment, but no differences between the groups ((Early Treatment Diabetic Study Research Group 1991) (Pahor 1998)).

Contrast sensitivity

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Characteristics of the studies investigating CS can be found in Table 2. 

Sivaprasad et al. (2017) also examined the changes in CS scores in patients with PDR receiving either PRP or aflibercept (see the section ‘Visual fields’ for study characteristics). CS letter scores were measured at baseline and 52 weeks and did not differ between the two groups (PRP: \(-1.0 \pm 0.5\) letter score vs. aflibercept: \(-0.5 \pm 0.5\) letter score, \(p=0.55\)).

Colour vision

Characteristics of the study investigating CV can be found in Table 2. ETDRS group (1991) compared the effect of full-scatter PRP vs. mild-scatter PRP on CV in patients with moderate-to-severe non-proliferative DR or PDR. The patients had their CV measured at baseline, at eight months and 4 years (see the section ‘Visual fields’ for study characteristics). No differences between the two groups were found at either eight months or 4 years after treatment.

Risk of bias

Figure 2 shows the evaluation of the risk of bias in the ten included studies. Sivaprasad et al. (2017) was the only study without any risk of bias. Six studies (Muqit et al. 2010; Nagpal et al. 2010; Muqit et al. 2013; Gross et al. 2015; Sivaprasad et al. 2017; Gross et al. 2018) had an appropriate sequence generation and allocation concealment where the rest did not report their randomization process and/or allocation concealment. Risk of detection bias with no blinding of outcome assessment was high in most studies except for Muqit et al. (2010) and Sivaprasad et al. (2017) who masked/blinded the staff who analysed/assessed the data. Risk of attrition bias was medium with studies with low attrition bias and the rest with an unknown or high risk. Risk of reporting bias was unknown in most cases except for Gross et al. (2015 and 2018) and Sivaprasad et al. (2017) where study protocols were available.

Discussion

In this systematic review we compared treatment induced side effects (VF, dark adaptation, CV and CS) in patients with PDR treated with conventional PRP versus other treatments. Overall, we found that most studies investigated VF, which was affected by both PRP and different approaches to laser treatment. However, there were no differences in side effects between treatment groups.
Furthermore, we found that most studies that compared VEGF inhibitors with PRP found less damage to VF in patients receiving VEGF inhibitors. The study that investigated CS found early, but no long-term changes. Regarding CV one study found no changes after PRP.

The studies included in this systematic review were very heterogeneous and therefore difficult to compare, and unfeasible to do a meta-analysis of.

**Visual fields: conventional PRP vs. VEGF inhibitors**

Four studies investigated VF as a side effect to treatment in conventional PRP vs. VEGF inhibitors (Jampol et al. 2017; Gross et al. 2015; Gross et al. 2018; Sivaprasad et al. 2017). These studies found that VEGF inhibitors were less damaging on VF than PRP after one and two years. However, in Gross et al. 2018 5 years follow-up these differences between groups did not persist.

The studies were overall well-constructed, had a large number of participants, and a long follow up period (52 weeks to 5 years). The studies had an overall low risk of bias which makes the evidence strong. However, some concerns regarding the studies were found. There was a tendency of patients with a low visual acuity and high HbA1c to be excluded. This exclusion is critical as it gives a risk that the results can only be applied to patients with a certain visual acuity and HbA1c as it does not give a wide representation of the PDR population. As a consequence, one could suggest that these results only apply to a specific part of the PDR population. Furthermore, Gross et al. 2015 supplied treatment of 72 of the 203 eyes in the PRP group with VEGF inhibitors at BL. Previous studies has shown a beneficial effect of the combination of VEGF inhibitors and PRP in regards to visual acuity (Zhou et al. 2016; Figueira et al. 2018) but no studies on the effect on VF of this combination has been conducted. It is therefore unknown how it affects the VF compared to treatments alone with VEGF inhibitors or PRP. It is therefore also unknown if the supplement of VEGF inhibitors in the Gross et al. 2015 study could have led to potential bias because of the combination of treatments.

The Gross et al. 2018 study had a high a high loss to follow up. As the authors states themselves, the results of no differences in the 30-2 VF at 5 years must therefore be interpreted with caution. In perspective, previous studies with long-term follow up have shown that visual fields in patients with different levels of diabetic retinopathy deteriorate over time, even though no PRP has been applied (Hellgren et al. 2013; Hellgren et al. 2014). This long-term change is an interesting angle as
one could speculate if the catch-up in the groups after 5 years is simply because of the natural progression of the disease, and not the treatment itself.

Sivaprasad et al. (2017) did not exclude patients that had previously received PRP which also could have affected their results. If a true perspective of the effect of PRP on visual field should be present, the patients should not previously have received PRP, as one cannot say if it is the present or previous treatment with PRP that gives the outcome found.

Visual fields: conventional PRP vs. other approaches

Six studies compared different approaches to lasers effect on VF (Buckley et al. 1992; Muqit et al. 2010; Muqit et al. 2013; Pahor et al. 1998; ETDRS group 1991; Nagpal et al. 2010). These studies found that lasers affect VF, but they did not find any differences between the approaches. The studies methods, follow up time and number of participants varied a lot. There was a spread in bias from low to a high risk (Figure 2). Buckley et al. (1992), Muqit et al. (2010), Nagpal et al. (2010) and Muqit et al. (2013) had a follow up time from one month to twelve weeks. This is a short follow up period as damages to the retina as a consequence of PRP was previously detected after longer periods of time (Kim 2012). None of the studies found any differences between the different groups, which maybe could have been the case, if follow up time was longer. Buckley et al. (1992) did not exclude patients that previously had received PRP. This could potentially have influenced the results of this study in the same way as mentioned for the Sivaprasad study.

The studies comparing mild- vs. full-scatter PRPs effect on VF (Early Treatment Diabetic Study Research Group 1991; Pahor 1998) was very different in terms of follow up (four years vs. one month). The ETDRS group is a study of older date, but a very strong study with a lot of participants, a low drop-out rate and a long follow up which makes the results convincing. Both studies showed worsening of VF, but no differences were found between the two groups of both short- and long-term follow up. These findings are in line with other studies where different approaches to PRP showed no differences in the affection of VF (Muqit et al. 2010; Nagpal et al. 2010; Moutray et al. 2018). These results indicate that PRP is harming the retina regardless the method used.

Colour vision and contrast sensitivity

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One study investigated CV as a side effect to treatment of PDR (Early Treatment Diabetic Study Research Group 1991) and one study investigated CS as a side effect to treatment of PDR (Sivaprasad et al. 2017). As mentioned in the previous sections, both studies were assessed as strong studies that was well constructed and had a high number of participants. No differences between the treatments was found in either side effect, one or four years after treatment.

CS has shown to be lower in patients with type 2 diabetes with and without DR (Sokol et al. 1985) and to be affected in patients immediately after PRP, but not long-term (Khosla et al. 1994). When applying PRP, it is the peripheral photoreceptors and RPE that gets affected (Stefansson 2006). In the retinal periphery, only low frequency channels are present, thus the peripheral retina is only able to detect low frequencies when testing CS. When measuring CS at low frequencies, the rods are suppressed and only the cones are tested (Arden 1978). As the cones are still present in the centre part of the retina and especially in the fovea, after PRP, this could maybe be the reason that no differences between the two groups were detected in CLARITY (Sivaprasad et al. 2017).

CV has also shown to be affected by full-scatter PRP (Khosla et al. 1994; Fong et al. 2007). The ETDRS group did not find any long-term differences between full-scatter and mild-scatter PRP suggesting that laser-treatment to the retina is damaging for CV either way it is applied. However, no determinate conclusions can be made on the results of only one study on each field.

**VEGF inhibitors vs. PRP**

The results from the four studies investigating VEGF inhibitors vs. PRP points towards a less harming effect of VEGF inhibitors as a treatment of PDR when it comes to VF as a side effect. This is of course important for patients in the matter of in example keeping their driver-license but also to keep the best possible vision. There are undoubtedly a lot of benefits of VEGF inhibitors as it has shown a great effect in the treatment of PDR (Arevalo et al. 2017; Figueira et al. 2018; Bressler et al. 2019) and, as found in this study, a trend toward smaller risk of side effects. Despite the positive effects of VEGF inhibitors, one should be careful before using this treatment solely as it requires a continuously large number of well-timed injections. This gives the pitfall of potential compliance and patients not either receiving the treatment in time, or not at all. Because of this, PRP is shown to be a better treatment when it comes to patients with compliance because of the relatively few treatment sessions and long-term effect (Obeid et al. 2018). As an answer to this...
problem, as examined in many studies (Zhou et al. 2016; Dehghani et al. 2017; Sameen et al. 2017; Ali et al. 2018; Figueira et al. 2018), PRP combined with VEGF inhibitors could be a proposed solution to assure efficient and long-term treatment of PDR. Furthermore, treatment with VEGF inhibitors can cause complications such as endophthalmitis, lens damage and retinal tears and this should be reflected upon if chosen for the treatment of PDR.

Visual function in patients with diabetes

As mentioned, VF have shown to be affected in patients with DR, even before receiving PRP (Chee & Flanagan 1993; Henricsson & Heijl 1994; Hellgren et al. 2013; Hellgren et al. 2014; Boynton et al. 2015). When DR progresses to PDR and treatment with PRP is required it has the potential to further decreasing the VF, making the conditions for the patient even worse. As we have found in this study, VF seems to be less affected by VEGF inhibitors compared to PRP. However, more functions are yet to be discovered. In previous studies exploring night vision in patients with diabetes, it was found that an increasing grade of DR leads to impaired dark adaptation (Henson & North 1979; Hsiao et al. 2019). As previously mentioned, PRP is known to decrease night vision (Boynton et al. 2015) but in the search conducted for this we did not find any RCTs or prospective studies comparing different treatments effect on dark adaptation. We also only found one study that investigated CV and CS. This leaves these fields yet to be fully explored before being able to make any conclusions.

Another approach that is interesting to discuss is electroretinographic (ERG) changes in the treatment of PDR. ERG is a diagnostic tool that measures the electrical activity of the retinal cells. This activity is formed as a response to light. The visual function has previously been investigated with ERG in patients with PDR treated with PRP and VEGF-inhibitors. These studies found that a less extensive approach of PRP combined with VEGF-inhibitors and VEGF-inhibitors as a solo treatment caused less affection to visual function, measured as ERG compared to PRP (Messias et al. 2012; Messias et al. 2018). ERG offers a physiological examination of the specific cells in the retina and an insight to the function of these. Studies propose that PRP not only destroys the cells where the laser beam hits, but also harms adjacent tissue (Schuele et al. 2005) which in that connections leads to the worse outcome in ERG measurements. ERG changes could have been
relevant to examine in this review, however we aimed for a more clinical approach and therefore focused on more clinical examinations such as loss of VF.

**Clinical applicability**

Even though there was a high loss to follow up, the 5 years follow up from DRCR.net Protocol S and the 2 years follow up from the CLARITY study has shown promising results on the long-term effectiveness with similar results regarding visual acuity, macular oedema, visual fields and risk of vitreous haemorrhage for VEGF inhibitors vs. PRP. The results of these studies should be considered when choosing treatment for PDR, as they are of a substantial nature because of the high number of subjects and the low risk of bias in both study designs. However, several factors are to be considered when choosing the optimal treatment of PDR for each patient. As mentioned, the compliance of the patient is important to consider. If VEGF inhibitors are chosen as a solo treatment, it is essential to know that the patient is consistent in their visits to receive treatment.

Another important aspect to consider is the financial cost of treatments. VEGF inhibitors have been considered less desirable when it comes to cost effectiveness compared to PRP and it has been argued that the use in PDR cannot be justified on this fact (Maniadakis & Konstantakopoulou 2019). The high cost of treatment with VEGF inhibitors poses an obstacle against implementing it in the real world, as many countries have limited health-care options. PRP has been used for many years, and long-term treatment effectiveness in avoiding PDR related complications is evident. Though, if side effects are of importance for the patient and practitioner, it is worthwhile to consider treatment with VEGF inhibitors supplemented by a less extensive laser treatment to avoid side effects but still have some degree of long-term effect of treatment.

Another important clinical aspect to consider is the transferability of statistical differences in VF between different treatments to the patient’s own perception of visual quality. It is not certain that a statistically significant difference is appreciated by patients, why it should be considered to measure on i.e. VF in relation to driving ability as this carries a high value for a big group of patients (Liddle et al. 2012). Questionnaires would also be a good supplement to VF measurements to test if the patient’s own perception comes hand in hand with measured differences.
Limitations
One limitation to this study was the absence of a meta-analysis of the included studies. However, this was not feasible as the studies included in this review were testing different treatments effect on side effects. This makes it impossible to do quantitative analysis on the results. It is also not possible to compare different side effects to each other. Furthermore, different methods for testing of visual field were also used. It is therefore difficult to compare the results of the included studies directly. Additionally, a lot of the included studies had a small number of participants and a short time of follow up making the evidence of these studies less strong. Some of the studies had an inclusion of patients with NPDR. This could make the results apply to a bigger population and not only patients with PDR. Furthermore, we did not distinguish between low or high-risk PDR which could have made the distribution of side effects different between different levels of PDR, as a natural course of the disease.
As only one study on CS and one on CV was assessed it was impossible to conclude anything about these aspects, making this part of the study unreliable.

No studies investigating dark adaptation could be included in this study, making this part of the field yet to be discovered. The review is limited to specific side effects and further functions such as ERG could also have been relevant to examine.

Conclusions
PRP is known to cause side effects as loss of visual field and night vision. In this systematic review exploring certain side effects to treatments of proliferative diabetic retinopathy, it was found that there was a trend, confirmed in four large studies, towards VEGF inhibitors causing less harm to VF compared to conventional PRP. However, patient compliance and risk factors of VEGF inhibitor treatment should be strongly considered when choosing what treatment is right for each patient.
We did not find any definitive evidence to be able to make final conclusions about the effect of different approaches to laser on VF, due to high risk of bias and heterogeneity of the studies. Furthermore, it was not possible to make certain conclusions of either CV or CS as we only found one study exploring each field that fulfilled the inclusion criteria for this study.
For future perspectives, it could be interesting to investigate other treatments effect on other side effects than VF, especially VEGF inhibitors or less comprehensive approaches to PRP. We
encourage that further studies on this subject is done as randomized controlled trials with a high number of participants, and that further side effects such as night vision is to be explored in this manner.

Acknowledgment
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Reference list


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Figure 1: Study flow diagram
Figure 2: Risk of bias
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**Figure legends**

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Figure 1: Study flow diagram with the selection process of the articles included in this study.

Figure 2: Cochrane risk of bias summary: review authors’ judgements about each risk of bias item for each included study. +: low risk of bias. ?: unclear risk of bias. -: high risk of bias.

Table 1: Characteristics of the included articles featuring visual fields

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Type of diabetes</th>
<th>Side effects investigated</th>
<th>Interventions and number (n) of included eyes</th>
<th>Follow up time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jampol et al. (2017)</td>
<td>Randomized controlled trial</td>
<td>Type 1 + 2</td>
<td>Visual fields (VF) (Humphrey) 30-2 + 60-4 (decibel (dB))</td>
<td>Total n=146, Ranibizumab n=77, PRP n=69</td>
<td>2 years</td>
<td>60-4 VF: PRP vs. Ranibizumab: -1.4 ± 2.0 dB vs. -0.4 ± 1.9 dB, p&lt;0.001</td>
</tr>
<tr>
<td>Gross et al. (2015)</td>
<td>DRCR.net Protocol S</td>
<td>Randomized controlled trial</td>
<td>VF (Humphrey) 30-2 + 60-4 (dB)</td>
<td>Total n= 394, Ranibizumab n= 191, PRP n= 203</td>
<td>2 years</td>
<td>- 60-4 VF: PRP vs. Ranibizumab: -261±280 dB vs. -29±209 dB, p&lt;0.001, -30-2 VF: PRP vs. Ranibizumab: -146±311 dB vs. 9±209 dB, p=0.001</td>
</tr>
<tr>
<td>Gross et al. (2018)</td>
<td>DRCR.net Protocol S</td>
<td>Randomized controlled trial</td>
<td>VF (Humphrey) 30-2 + 60-4 (dB)</td>
<td>Total n= 394, Ranibizumab n= 191, PRP n= 203</td>
<td>5 years</td>
<td>- 60-4 VF: PRP vs. Ranibizumab: -348±367 dB vs. -199±349 dB, p=0.03, -30-2 VF: PRP vs. Ranibizumab: -190±333 dB vs. -157±334 dB, p=0.64</td>
</tr>
<tr>
<td>Sivaprasad et al. (2017)</td>
<td>CLARITY</td>
<td>Randomized controlled trial</td>
<td>VF (Esterman missed spots (mis))</td>
<td>Total n= 232, Aflibercept n= 116, PRP n= 116</td>
<td>52 weeks</td>
<td>- Binocular Esterman: PRP vs. Aflibercept: 3.2±0.8 mis vs. 0.2±0.8 mis, p=0.007, -Uniocular Esterman: PRP vs. Aflibercept: 3.9±0.9 mis vs. 1.9±0.8 mis, p=0.12</td>
</tr>
</tbody>
</table>
Muqit et al. (2010) | Randomized controlled trial | Type 1 + 2 | VF (Humphrey) 24-2 (dB) and Esterman (binocular) | Total n=40 | 12 weeks | SS-PRP: Baseline vs. 12 weeks 24-2 VF: -5.94±2.9 dB vs. -5.21 dB, p<0.05 - MS-PRP: Baseline vs. 12 weeks 24-2 VF: -4.62±3.5 dB vs. -5.04 dB, p=0.24 No differences between the two groups were found.

Muqit et al. (2013) | Randomized controlled trial | Type 1 + 2 | VF (Humphrey) 24-2 MD (dB) | Total n=30 | 12 weeks | TRP 12 weeks 24-2 VF: +0.70 dB±1.0, p=0.07 - MT-PRP 12 weeks 30-2 VF: +0.88 dB±0.9, p=0.015 - SI-PRP 12 weeks 30-2 VF: +1.0 dB±0.9, p=0.02 No differences between the three groups were found.

ETDRS group (1991) | Randomized controlled trial | n.a.* | VF (Goldmanns I/4e and I/4 test) | Total n=1128 | 4 years | I/4 VF: Worsened in both groups (p<0.001) No differences between the two groups were found.

Nagpal et al. (2010) | Randomized controlled trial | n.a.* | VF (Humphrey) 30-2 (dB) | Total n=120 | 6 months | Zone A 30-2 VF: p=0.26 Zone B 30-2 VF: p=0.09 No differences between the two groups were found.

Pahor (1998) | Prospective | n.a.* | VF (Humphrey) central 30-1 (MD) and peripheral 30/60-1 | Total n=40 | 1 month | Full-scatter: Baseline vs. 4 years 30-1 VF: -4.84±2.65 vs. -7.61±4.16, p<0.05 - Mild-scatter: Baseline vs. 4 years 30-1 VF: -3.73±2.62 vs. -5.21±2.81, p<0.05 No differences between the two groups were found.
<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
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<th>Interventions and number (n) of included eyes</th>
<th>Follow up time</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Buckley (1992)</td>
<td>Prospective</td>
<td>Type 1 + 2</td>
<td>VF (Humphrey) full field (% gain/loss)</td>
<td>Total n=46 Argon laser superiorly, diode laser inferiorly n=7 Diode laser superiorly, argon laser inferiorly n=8 Control group (non-diabetic) n=24 Control group (diabetic) n=7</td>
<td>Six weeks</td>
<td>- Absolute loss argon vs. diode VF % loss: 9.00% vs. 10.86%, p=0.663</td>
</tr>
<tr>
<td>Sivaprasad et al. (2017)</td>
<td>Randomized controlled trial</td>
<td>Type 1 + 2</td>
<td>Contrast sensitivity letter scores (Pelli Robson) (letter score (LS))</td>
<td>Total n= 232 Aflibercept n= 116 PRP (panretinal photocoagulation) n= 116</td>
<td>52 weeks</td>
<td>PRP vs. Aflibercept: -1.0±0.5 LS vs. -0.5±0.5 LS, p=0.55</td>
</tr>
<tr>
<td>ETDRS group (1991)</td>
<td>Randomized controlled trial</td>
<td>n.a. *</td>
<td>Colour vision (Farnsworth-Munsell 100 Hue Test) (error score)</td>
<td>Total n=1128 Full-scatter PRP n= 538 Mild-scatter PRP n= 590</td>
<td>4 years</td>
<td>No differences found.</td>
</tr>
</tbody>
</table>

*n.a.: not announced.

Table 2: Characteristics of the included articles featuring contrast sensitivity and colour vision