Evidence and indications for systemic treatment in diabetic retinopathy

a systematic review

Elkjaer, Anna Sofie; Lynge, Sidsel Kirstine; Grauslund, Jakob

Published in:
Acta Ophthalmologica

DOI:
10.1111/aos.14377

Publication date:
2020

Document version:
Accepted manuscript

Citation for pulished version (APA):
Elkjaer, A. S., Lynge, S. K., & Grauslund, J. (2020). Evidence and indications for systemic treatment in diabetic retinopathy: a systematic review. *Acta Ophthalmologica*, *98*(4), 329-336. https://doi.org/10.1111/aos.14377

Title

Evidence and indications for systemic treatment in diabetic retinopathy: a systematic review

Authors

Anna Sofie Elkjaer*[1,2]

Sidsel Kirstine Lynge*[1,2]

Jakob Grauslund[1,2,3]

* Shared first authorship

1: Department of Ophthalmology, Odense University Hospital, Odense, Denmark.

2: Research Unit of Ophthalmology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

3: Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark.

Corresponding author

Professor Jakob Grauslund, MD, PhD, DMSci

Department of Ophthalmology

Odense University Hospital

Sdr. Boulevard 29

DK-5000 Odense C, Denmark

Phone: +45 65 41 27 82

Fax: +45 66 12 63 87

E-mail: jakob.grauslund@rsyd.dk

Key words:

Diabetic retinopathy

Systemic therapy

Systematic review

Abstract:

Purpose: Eye screening is mandatory in diabetes, but treatment is only indicated at the sight-threatening stages of diabetic retinopathy (DR). Treatments include intravitreal injections, laser photocoagulation, and vitrectomy, which are all invasive options. In order to prevent or delay DR, it is important to investigate earlier, non-invasive managements prior to sight-threatening DR. The aim of this study is to evaluate the effect of systemic treatment on incident and progressive DR in diabetes.

Methods*:* The search in this systematic review was performed in Pubmed and Embase using the keywords "diabetic retinopathy" AND "systemic therapy". Two independent researchers identified 619 studies; 26 duplicates were removed, 579 articles were excluded based on title and abstract, and six were removed after full text assessment. Five articles were added from reference screening, resolving in a total of 13 eligible articles. These were quality-assessed using the Cochrane Risk of Bias tool.

Results: We included 12 randomized control trials and one follow-up study. Intensive glycemic control (IGC), antihypertensive and lipid lowering treatments were some of the main interventions tested in the studies. Three studies found statistically significant reduction of progression of DR by IGC, three by antihypertensive, and two by the lipid lowering drug, fenofibrate.

Conclusion*:* Systemic intervention appears important in different stages of DR. While IGC seems effective in relation to incident and progressive DR, antihypertensive treatments may be valuable in the early stages of DR, as opposed to fenofibrate, which could benefit at a later stage.

Introduction:

The prevalence of diabetes is increasing worldwide, and approximately 642 million people will have diabetes in the world in 2040.(Malyankar et al. 2000) Diabetic retinopathy (DR) is the most frequent microvascular complication in diabetes, as well as a leading cause of blindness among people aged 30-69 years.(Beulens et al. 2009) DR results from microvascular retinal damage, which may lead to diabetic retinal ischemia, increased vascular permeability, retinal neovascularization and diabetic macular oedema (DMO). DR can be classified as non-proliferative (NPDR) and proliferative DR (PDR), where NPDR is divided into mild, moderate and severe NPDR.(Corcostegui et al. 2017) The main risk factors for DR are type and duration of diabetes, hyperglycemia and elevated blood pressure (BP).(Yau et al. 2012) Current treatment options for DR include laser photocoagulation, intravitreal therapy, and vitrectomy. Treatment is, however, only indicated at the sight-threatening stages of DR (PDR and DMO). Likewise, there are numerous potential side effects given the invasive nature of the treatments. Therefore, it will be relevant to evaluate if systemic treatment could prevent or arrest DR at the early stages. Hence, the aim of this systematic review was to evaluate the effect of systemic therapy to prevent incident or delay progressive DR.

Methods:

The PICO-model (O'Sullivan et al. 2013) was used to identify the population, intervention, comparison and outcome of interest. The eligibility criteria for the studies were prospective studies of patients with diabetes (population), who had a systemic treatment (intervention). Comparison was placebo or standard treatment, and outcome was preferred to be progression, incidence or regression of DR. Two authors (ASE and SKL) searched separately to identify suitable subject headings and keywords. From the findings of these searches, a common search strategy was chosen: “diabetic retinopathy” AND “systemic therapy”. This search strategy was used in the two databases, Embase and PubMed. Different filters were added; Language: English and Study type: humane.

The search gave 619 hits, which were all imported to Covidence (Covidence 2019) via Endnote.(Green 2008) Duplicates were deleted, leaving 593 articles. These were assessed first by title and abstract; 579 articles were found irrelevant and were excluded. The rest of the articles were assessed by full text. Six were excluded as they did not meet the PICO specifications. All assessments were done separately by each author, and conflicts were solved in plenum. The

references of the studies were checked for relevant articles, if any was found they were added to Covidence and used. In the end, 13 articles were included.

It was an initial decision only to include studies less than 15 years old, with the purpose of finding newer research. However, during the assessment of references, this decision was reversed and five articles were added even though they were older than 15 years. This decision was taken since the studies turned out to lay the foundation for many of the treatments tested in newer studies. Pilot studies were not of interest, because of the small sample size.

When the eligible articles had been found, they were assessed individually by each author with the Cochrane risk of bias (ROB) tool,(Julian PT Higgins et al. 2019) and conflicts were solved in plenum. The quality assessment was focused into different topics and these were assessed and given a score of *low, unclear or high* risk of bias. At last, the scores of the different topics were translated into an overall score; *Good quality* if all topics had *low* risk of bias or maximum one *unclear* risk of bias. *Fair quality* if one topic had high risk of bias or maximum two topics had *unclear* risk. Lastly, *poor quality* if more than one topic had high risk of bias or more than two topics had *unclear* risk (Table 2).

While the aim of the study was illuminated using the evidence of the articles, the quality assessment was used to judge the validity of the studies.

Results:

In the field of systemic intervention to prevent DR, there are many different types of treatment strategies targeting systemic risk factors. Of 13 articles, we found 12 RCTs investigating treatments such as intensive glycemic control (IGC), BP lowering, and lipid lowering, but also more differentiated treatments (Table 1).

Intensive Glycemic Control:

The Diabetes Control and Complication Trial (DCCT) group examined whether IGC with insulin pump or injection decreased the frequency and severity of complications in type 1 diabetes.(DCCT. 1993) Patients without and with preexistent minimal DR were assigned into a primary and secondary intervention group and followed for a mean of 6.5 years. The goal of the IGC intervention was blood glucose level close to normal. During the study, median HbA1c in IGC group was 7% vs. 9% in the group receiving conventional therapy. In the primary prevention cohort, the cumulative incidence of DR was similar in the two groups until approximately 36

months of follow-up after which they started to separate. Over time, IGC (n=348) reduced the adjusted mean risk of DR with 76% (95% CI 65-85%) compared with conventional therapy (n=378).

In the secondary intervention cohort, IGC patients had a cumulative higher incidence of sustained progression compared to conventional therapy during the first year, but a lower cumulative incidence after 36 months and until the end of the study. In this cohort IGC (n=363) overall slowed the progression of DR by 54% (95% CI 39-66%) and reduced the development of PDR or severe NPDR by 54% (95% CI 14-67%). There was a two-to-threefold increase in severe hypoglycemia in the IGC group.

The article was of *fair quality.*

The Epidemiology of Diabetes Interventions and Complications (EDIC) study was an observational study and followed the DCCT cohort study, with 97% subjects (n=1,394) from the DCCT participating.(Aiello 2014) All patients, whether they belonged to the former IGC group or control group, were assigned to IGC treatment, and mean HbA1c in the two groups converged to approximately 8%. At year 10 in the EDIC study, there was a continued risk reduction of 56% ($p<0.001$) in the development of PDR in the group that had received IGC during DCCT. Odds reduction for other endpoints including onset of severe NPDR or worse was 58% ($p< 0.001$), and onset of PDR or worse was 58% ($p<0.001$).

The article was of *fair quality.*

The United Kingdom Prospective Diabetes Study (UKPDS) studied the risk of microvascular and macrovascular complications in patients with type 2 diabetes in either IGC or conventional treatment.(UKPDS. 1998) Follow-up mean was 10 years and interventions in the intensive group were either sulphonylurea (n=1573) or insulin (n=1156). Reduction of HbA1c was seen in the IGC group (7.0%) compared with the conventional group (7.9%). In the IGC group, the risk was 12% lower (95% CI 1-21%, p=0.029) for any diabetes-related endpoint compared with the conventional group. Most of the risk reduction in any diabetes-related aggregate endpoint were found in microvascular endpoints, which had a total reduction of 25% (95% CI 7-40%, p=0.0099).

The article was of *fair quality.*

Blood pressure treatment:

Chaturvedi et al. analyzed whether four years of treatment with candesartan reduced the incidence and progression of DR in type 1 diabetes.(Chaturvedi et al. 2008) This was done in the Diabetic Retinopathy Candesartan Trials 1 (DIRECT-1). The participant had to be normotensive with a BP≤130/85 mm Hg. There was a tendency towards a reduced incidence of DR (hazard ratio [HR] 0.82, 95%CI 0.67-1.00, p=0.0508) but not progression (HR 1.02, 95% CI 0.80-1.31, p=0.85) in the candesartan group.

The article was of *good quality.*

The effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes study (EUCLID investigated the effect of the angiotensin converting enzyme (ACE) inhibitor lisinopril (n=202) compared to placebo (n=207). (Chaturvedi et al. 1998) Subjects were normotensive with a BP≤155/75-90 mmHg, and the follow-up period was two years. At baseline, 59% of subjects in the invention group and 65% in the placebo group had DR. Progression of DR of at least one level was found in 13.2% of subjects with lisinopril and 23.4% of subjects on placebo. Odds ratio [OR] was 0.50 (95% CI 0.28-0.89, p=0.02), and adjusted OR [aOR] was 0.55 (95% CI 0.29-1.05, p=0.07).

The article was of *fair quality.*

RASS investigated the effect of renin-angiotensin system (RAS) blockade on both renal and retinal morphologic features in normotensive patients (BP≤135/85 mmHg) with type 1 diabetes.(Mauer et al. 2009) Subjects were randomly assigned to one of three treatments: enalapril, an ACE inhibitor (n=94); losartan, an angiotensin receptor blocker (ARB) (n=96), or placebo (n=95). Follow-up was five years. DR progression, defined as two steps or more, was reduced in both the enalapril (OR 0.35, 95% CI 0.14-0.85, p=0.02) and the losartan group (OR 0.30, 95% CI 0.12-0.73, p=0.008) compared with placebo. This was independent of changes in BP.

The article was of *good quality.*

The DIRECT-2 study,(Sjolie et al. 2008) investigated whether candesartan treatment (n=951) could slow progression and induce regression of DR compared to placebo. Subjects were type 2 diabetes patients who were normotensive patients (BP≤130/85 mmHg) without

antihypertensive treatment and hypertensive patients (BP≤160/90 mmHg) in antihypertensive treatment. The follow-up period was at least four years. While DR progression was not reduced with candesartan, DR-regression was statistically significantly increased with candesartan (HR 1.34, 95% CI 1.08-1.68, p=0.009).

The article was of *good quality.*

In UKPDS,(UKPDS. 1998) the effect of tight BP control was tested in hypertensive patients with type 2 diabetes. Mean follow-up was 8.4 years. The tight BP control group (n=758) was given either ACE inhibitor captopril or beta-blockers with the aim of a BP<150/85. Tight BP control reduced the risk of diabetes-related-endpoints (p=0.0046), deaths related to diabetes (p=0.019), strokes (p=0.013), and microvascular end points (p=0.0092).

The article was of *fair quality.*

Fenofibrate treatment:

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, Keech et al. (2007) investigated whether long-term therapy with fenofibrate (n=4895) reduces progression of DR and need for laser treatment in patients with type 2 diabetes after five years compared to placebo (n=4900). Fenofibrate is a peroxisome proliferator-activated receptor agonist, which lowers VEGF, total-cholesterol, triglyceride, low-density-lipoprotein (LDL) and increases apolipoprotein A-I and high-density-lipoprotein (HDL). Furthermore, it seems to have beneficial effect on inflammation and thrombogenesis. (Wright & Dodson 2011; Sharma et al. 2015)

In patients with pre-existing DR, statistically significantly fewer in the fenofibrate arm had progression of as compared to patients treated by placebo. However, the ocular outcome did not differ between the two groups overall or in the subset of patients without pre-existing DR. An exploratory composite endpoint of two step progression of DR grade, DMO, or laser treatments were lower in the fenofibrate group than in the placebo group (HR 0.66, 95% CI 0.47–0.94, p=0.022). The requirement for first laser treatment for all DR was lower in the fenofibrate group than placebo group (HR 0.69, 95% CI 0.56-0.84, p=0.0002).

The article was of *fair quality.*

Combination trials:

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study included an ocular substudy, AdRem, which investigated the 4-year effect of BP treatment and IGC treatment on incidence and progression of DR in type 2 diabetes.(Beulens et al. 2009) The BP treatment was with a fixed dose of perindopril–indapamide and the mean baseline BP was 143/79 mmHg. Compared with placebo, there were no statistically significantly effect of BP treatment (n=623) or IGC (n=630) on incidence or progression of DR. However, BP lowering treatment reduced the incidence of DMO (OR 0.50, 95% CI 0.29-0.88, p=0.016) and arteriovenous nicking (OR 0.60, 95% CI 0.38-0.94, p=0.025) compared with placebo.

The article was of *good quality.*

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study investigated whether IGC (n=1429, target HbA1c<6%) compared with standard therapy, combination therapy for dyslipidemia (n=806, 160 mg fenofibrate + simvastatin) compared with simvastatin, and BP-lowering treatment (n=647) compared with standard therapy, limited the progression of DR in type 2 diabetes after four years.(Chew et al. 2010) Baseline mean glycated hemoglobin was 8.2%, mean HDL=41.9 mg/dl, LDL=100.7mg/dl and mean BP=135/75.

IGC (adjusted OR 0.67, 95% CI 0.51-0.87, p=0.003) and treatment of dyslipidemia (adjusted OR 0.60, 95% CI 0.42-0.87, p=0.006) reduced the rate of progression of DR compared with standard therapy or placebo. On the other hand, BP lowering treatment did not reduce DR (adjusted OR 1.23, 95% CI 0.84-1.79, p=0.29).

The article was of *fair quality.*

Divergent treatment types:

In subjects with DMO, Campochiaro evaluated the efficacy and safety of different doses of Protein kinase C (PKC) 412 inhibitor (n=107) compared to placebo (n=34).(Campochiaro 2004) The follow-up period was 12 months. PKC412 inhibitor is a nonspecific kinase that suppresses vascular endothelial growth factor induced neovascularization and retinal leakage.

A decrease in retinal thickening (judged from fundus photographs) with 150 mg/d of PKC412 (p=0.032), and with the higher doses by OCT ($p \leq 0.039$) was found. There was a statistical significance difference in the high-dose group from that in the placebo group. In total, 63-73%

exhibited no shift in DR classification, 13-20% in each group showed a favorable shift from the initial screening, and 7–20% experienced a worsening in DR varied among treatment groups. Among treatment groups, no statistically significant differences were seen in the change in DR classification. The 150-mg/kg group showed significantly less retinal volume than the placebo group at three months. There was a small improvement in visual acuity at three months, compared with baseline visual acuity in the 100-mg/d PKC412 group (p=0.007).

The article was of *fair quality.*

Campochiaro also examinated the effect of AKB-9778 in a phase 3 study in patients with type 1 or 2 diabetes.(Campochiaro et al. 2016) AKB-9778 was tested alone (n=46) or in combination with ranibizumab (n=48) after three months of treatment and two months of follow-up in patients with DMO. They found statistically significant higher reduction from baseline central subfield thickness (CST) in the combination group compared to monotherapy with ranibizumab. Mean CST at week 12 and percentage of eyes with resolved edema in combination group was 340±11.2 and 29.2 % vs 392.1±17.1 and 17% in ranibizumab group. No statistically significant improvement in BCVA was seen between groups. There was, however, no difference in >2 steps improvement in DR severity score among the treatment groups.

The article was of *fair quality.*

Discussion:

At the moment, treatment of DR is only indicated at the time of sight-threatening complications. The possibility of preventing or delaying DR at an early stage could be of great interest, given that all treatment options are invasive, induce a considerable treatment burden, and come with a potential risk of side effects. There is some indication that systemic treatment is a possible way of treating different elements of DR either by slowing progression, reducing incidence, or by inducing regression. IGC, antihypertensive drugs and treatment with fenofibrate provide some evidence for this, but interesting results are also found in more divergent treatments like PKC12 and AKB-9778.

In the articles processed in this study, the systemic treatments take different forms. Most studies included tablets which make it possible for patients to be treated at home instead of undergoing intrusive intervention. Subcutaneous injection was also tested, which may limit potential side effects, since this treatment does not pass through the gastrointestinal channel.

Although this is interesting, there is a question of compliance with the risk of failure to use treatment or using it wrongly.

High blood glucose can weaken and damage the small blood vessels within the retina. Five of the articles concerned the effect of IGC.(DCCT. 1993; UKPDS. 1998; Beulens et al. 2009; Chew et al. 2010; Aiello 2014). These have been judged to be of *good* and *fair* quality and the results are therefore rated as valid. ACCORD-EYE and UKPDS, (UKPDS. 1998; Chew et al. 2010) found a reduction of DR-progression compared to placebo. In AdRem, (Beulens et al. 2009) a non-significant reduction in incidence and progression of DR were observed. ACCORD-EYE did not use a specific type of drug in the IGC group, but the patients were treated to HbA1c<6%.(Chew et al. 2010) The intervention group in DCCT was treated to have the same HbA1c level. In AdRem, patients were treated with a long-acting sulfonylurea, oral-glucose lowering agents and insulin to lower their HbA1c<6.5%. These findings indicate that there might be an ocular advantage of lowering the HbA1c below to < 6% for the eye. In the EDIC study,(Aiello 2014) it was observed that despite a comparable HbA1c level in the intervention and control group, there was a continuous beneficial effect of prior strict glycemic control. This phenomenon has been termed “metabolic memory”. Although intensive HbA1c lowering seems beneficial for the eye, higher risks of hypoglycemic events and mortality should also be taken into account.(DCCT. 1993; Arnold & Wang 2014)

Increased blood flow caused by increased blood pressure can damage the retinal capillary endothelial cells in people with diabetes. Antihypertensive treatment is associated with improved vascular structure and may reduce progression of DR.(Gillow et al. 1999) Eight of 13 articles investigated antihypertensive treatments, and of most of these were of *good* or *fair* quality, emphasizing the findings as reliable. Most found a reduced progression of DR compared to control. Only RASS and UKPDS found statistically significant reduction of progression of DR with this treatment.(UKPDS. 1998; Mauer et al. 2009) However, this was not primary outcome of the studies, which may limit the conclusions. The EUCLID study also found statistically significant reduction of progression of DR, but not when adjusted for center and baseline characteristics (Chaturvedi et al. 1998)**.** Likewise, DIRECT 1 and 2 did not meet the principal endpoints, although interesting results were observed.(Chaturvedi et al. 2008; Sjolie et al. 2008) In specific, DIRECT found a reduced rate of incidence and regression of DR in patients with mild to moderate DR.(Chaturvedi et al. 2008; Sjolie et al. 2008) More than half of the subjects in DIRECT-2 had Early Treatment of Diabetic Retinopathy Study [ETDRS] score of 35 or more (moderate DR or

worse). In DIRECT PROTECT 1, the same was observed, even though the mean age was much younger, and they had lower BMI and cholesterol level. The findings suggest that in type 1 diabetes, the treatment might be of importance in a stage before the development of DR, and in type 2 diabetes the treatment might improve pre-existing DR. Incidence of DR was not measured in DIRECT 2 because patients already had DR.(Sjolie et al. 2008) None of them found a statistically significant reduction of progression of DR with candesartan.

In AdRem,(Beulens et al. 2009) antihypertensive treatments reduced the occurrence of DMO and ICG reduced the risk of DMO. These interventions might be useful in patients to prevent DMO. In RASS (Mauer et al. 2009) and EUCLID(Chaturvedi et al. 1998) the patients were normotensive before the trial. This indicates that the outcome could be related to the medicine modifying the RAS-system, rather than the lowering of BP having an effect by itself.

Compared to normotensive patients in ACCORD-EYE and DIRECT,(Sjolie et al. 2008; Chew et al. 2010), UKPDS studied type 2 diabetic patients with severe hypertension at baseline.(UKPDS. 1998) Subject with higher BP were more likely to develop DR than subjects with lower. No relation of systolic BP at baseline and DR progression was seen. It therefore seems more beneficial to lower BP at severe hypertension rather than in the normal BP range, at least in type 2 diabetes. However, a positive effect on incidence was found in DIRECT-1, (Chaturvedi et al. 2008) and an effect on progression was found in RASS, (Mauer et al. 2009). Both were studying type 1 diabetes and included normotensive subjects only. The EUCLID(Chaturvedi et al. 1998) studied similar subjects and found an effect on progression, but not when adjusted for HbA1c.

Two of the articles investigated the effect of fenofibrate.(Keech et al. 2007; Chew et al. 2010) The mechanism of fenofibrate is more complex than serum lipid-lowering treatment. For instance, it is known that fenofibrate increases the circulating apolipoprotein A-I, which are independent protective factors in development of DR.(Sharma et al. 2015) Both studies were estimated to be of *fair* quality and considered to be reliable in their findings. Although in FIELD, the primary end point was need for laser treatment and not progression of DR,(Keech et al. 2007) the levels of DR in intervention and the control group were well balanced.

ACCORD-EYE was an ocular substudy of ACCORD study with DR as the primary endpoint.(Chew et al. 2010) However, subjects were taken from the ACCORD study and had high risk of cardiovascular disease or already had a cardiovascular disease at baseline. ACCORD-EYE found a significant reduced progression of DR with the treatment of simvastatin and fenofibrate in patients with dyslipidemia compared to simvastatin and placebo.(Chew et al. 2010) In comparison,

FIELD only found a reduced progression in normolipedemic patients with preexisting DR. The effect did not seem to be related to the concentrations of plasma lipids. In contrast, it seems to be related to stages of DR, with the most beneficial effect at the severe stages of DR.

In the PKC study,(Campochiaro 2004) progression of DR was not primary outcome, but no statistically significant differences in frequency distribution were seen in the change in DR classification between the treatment groups, which indicate that treatment did not have effect on progression. In the AKB-9778 study,(Campochiaro et al. 2016) there was an effect of subcutaneous injections with AKB-9778 on DMO by CST and BCVA, but no difference in improvement of DR between intervention groups. These two articles by Campochiaro have been estimated to be of *fair* quality.

Since DR is a disease with slow progression, it might take years to observe a result of a treatment. This is observed across the different types of treatments and studies. For instance, in UKPDS with antihypertensive treatment,(UKPDS. 1998) a deterioration in DR from baseline by two or more steps was seen after a median of 4.5 years of follow-up. In DIRECT-1 and DIRECT-2, reduction of incidence and regression are observed after at least four years.(Chaturvedi et al. 2008; Sjolie et al. 2008) In UKPDS, a continued reduction of DR during ten years of follow-up with IGC was observed.(UKPDS. 1998) In the DCCT, where IGC was the systemic intervention, it took three years to see an effect on patients, and a group of patients even had worsening in the first years (early worsening).(DCCT. 1993) None of the studies have an observed effect before three years have passed.

Some of the studies excluded a large number of patients which may reduce the possibility of generalization. In six studies, patients were excluded with hypertension, seven with history of heart disease, nine with renal impairment and three with hyperlipidemia. There was adjusted for other important baseline characteristics such as age, HbA1c, diabetes duration and type of diabetes in many of the studies, but still these factors vary between the studies. Two studies included both types of diabetes, where six included only type 2 and five type 1 diabetes. Some articles investigated patients with DMO. In most studies, patients were middle-aged, though they were a bit younger in five studies**.** These variations may also have affected the comparability of studies. Among the included studies three were conducted worldwide, four in the US only, two in USA and Canada, two in UK, one in Australia, Europe and North America, and one in Europe only.

Limitations for this systematic review include the inability to conduct a meta-analysis of the data, since the outcomes investigated in the articles were adverse. The articles deviated in

population characteristics, time for follow-up, measurement of outcome and endpoint definition, which would make them difficult to compare. Ten articles used the ETDRS as grading scale of progression, but defined progression with a different number of steps. Some articles had a small number of participants,(Campochiaro 2004; Mauer et al. 2009) which can lead to overestimation or underestimation of effect of intervention. In several studies, the participants were allowed to continue their usual medication, which could have impacted the outcome. However, most articles adjusted for differences in the control and intervention group, so that the groups were comparable within the studies.

Strengths of the study should also be acknowledged. Of the articles, 12 were RCTs, which is a high-rank study design. Of these, one article had an unclear risk of bias regarding the randomization strategy,(DCCT. 1993) where the others had low risk of bias. One was not a RCT but a follow-up study based on subjects from an earlier RCT.(Aiello 2014)
Another strength was that all the articles had low risk of bias in outcome blinding, which makes the outcomes more objective.

The search, screening of articles and quality assessments were performed by two reviewers independently, which make the process more objective. In the quality assessment of the articles, the ROB-tool was used to standardize the effort and the assessments were done individually by each reviewer as well. Although this effort was made, it should be noted that it could be impossible to avoid an element of subjectivity completely.

Conclusion:

In this systematic review, we found that systemic intervention can be useful in prevention of progression and incidence of DR. This was mainly seen in patients without PDR at baseline. Strict IGC can be effective in relation to progression but can be problematic because of the risk of hypoglycemic episodes. There is an indication that BP lowering treatment might be useful in the early stages of DR and it is most effective on progression in patients with high BP in type 2 diabetes. Fenofibrate might be more useful in the late stages of DR and had more effect on progression than simvastatin alone. In all treatment types, it was observed that the effect first appeared after three years. Additional long-term randomized trial would be important for further evaluation of the potential to delay of prevent sight-threatening DR as well as to determine which patients may particularly suited for such prophylactic treatment.

References

Aiello LP (2014): Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care **37**: 17-23.

Arnold LW & Z Wang (2014): The HbA1c and all-cause mortality relationship in patients with type 2 diabetes is J-shaped: a meta-analysis of observational studies. Rev Diabet Stud **11**: 138-152.

Beulens JW, A Patel, JR Vingerling, JK Cruickshank, AD Hughes, A Stanton, J Lu, GTSA Mc, DE Grobbee, RP Stolk, t AdRem project & Am committee (2009): Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. Diabetologia **52**: 2027-2036.

Campochiaro PA (2004): Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. Investigative ophthalmology & visual science **45**: 922-931.

Campochiaro PA, A Khanani, M Singer, S Patel, D Boyer, P Dugel, S Kherani, B Withers, L Gambino, K Peters, M Brigell & T-S Group (2016): Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression. Ophthalmology **123**: 1722-1730.

Chaturvedi N, M Porta, R Klein, T Orchard, J Fuller, HH Parving, R Bilous, AK Sjolie & DPS Group (2008): Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet **372**: 1394-1402.

Chaturvedi N, AK Sjolie, JM Stephenson, H Abrahamian, M Keipes, A Castellarin, Z Rogulja-Pepeonik & JH Fuller (1998): Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. Lancet (London, England) **351**: 28-31.

Chew EY, WT Ambrosius, MD Davis, RP Danis, S Gangaputra, CM Greven, L Hubbard, BA Esser, JF Lovato, LH Perdue, DC Goff, Jr., WC Cushman, HN Ginsberg, MB Elam, S Genuth, HC Gerstein, U Schubart & LJ Fine (2010): Effects of medical therapies on retinopathy progression in type 2 diabetes. New England Journal of Medicine **363**: 233-244.

Corcostegui B, S Duran, MO Gonzalez-Albarran, C Hernandez, JM Ruiz-Moreno, J Salvador, P Udaondo & R Simo (2017): Update on Diagnosis and Treatment of Diabetic Retinopathy: A Consensus Guideline of the Working Group of Ocular Health (Spanish Society of Diabetes and Spanish Vitreous and Retina Society). Journal of ophthalmology **2017**: 8234186.

Covidence (2019): Covidence: Better systematic review management.

DCCT. (1993): The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. . New England Journal of Medicine **329**: 977-986.

Gillow JT, JM Gibson & PM Dodson (1999): Hypertension and diabetic retinopathy--what's the story? The British journal of ophthalmology **83**: 1083-1087.

Green A (2008): Descriptive epidemiology of type 1 diabetes in youth: incidence, mortality, prevalence, and secular trends. Endocrine Research **33**: 1-15.

Julian PT Higgins, Jelena Savović, Matthew J Page & JA Sterne (2019): Revised Cochrane risk of bias tool for randomized trials (ROB2).

Keech AC, P Mitchell, PA Summanen, J O'Day, TM Davis, MS Moffitt, MR Taskinen, RJ Simes, D Tse, E Williamson, A Merrifield, LT Laatikainen, MC d'Emden, DC Crimet, RL O'Connell, PG Colman & Fs investigators (2007): Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet **370**: 1687-1697.

Malyankar UM, M Scatena, KL Suchland, TJ Yun, EA Clark & CM Giachelli (2000): Osteoprotegerin is an alpha vbeta 3-induced, NF-kappa B-dependent survival factor for endothelial cells. Journal of Biological Chemistry **275**: 20959-20962.

Mauer M, B Zinman, R Gardiner, S Suissa, A Sinaiko, T Strand, K Drummond, S Donnelly, P Goodyer, MC Gubler & R Klein (2009): Renal and retinal effects of enalapril and losartan in type 1 diabetes. The New England journal of medicine **361**: 40-51.

O'Sullivan D, S Wilk, W Michalowski & K Farion (2013): Using PICO to align medical evidence with MDs decision making models. Studies in health technology and informatics **192**: 1057.

Sharma N, J Ooi, J Ong & D Newman (2015): The use of fenofibrate in the management of patients with diabetic retinopathy: an evidence-based review. Australian Family Physician **44**: 367-370.

Sjolie AK, R Klein, M Porta, T Orchard, J Fuller, HH Parving, R Bilous, N Chaturvedi & DPS Group (2008): Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet **372**: 1385-1393.

UKPDS. (1998): UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet **352**: 837-853.

UKPDS. (1998): UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ **317**: 703-713.

Wright AD & PM Dodson (2011): Medical management of diabetic retinopathy: fenofibrate and ACCORD Eye studies. Eye (London, England) **25**: 843-849.

Yau JW, SL Rogers, R Kawasaki, EL Lamoureux, JW Kowalski, T Bek, SJ Chen, JM Dekker, A Fletcher, J Grauslund, S Haffner, RF Hamman, MK Ikram, T Kayama, BE Klein, R Klein, S Krishnaiah, K Mayurasakorn, JP O'Hare, TJ Orchard, M Porta, M Rema, MS Roy, T Sharma, J Shaw, H Taylor, JM Tielsch, R Varma, JJ Wang, N Wang, S West, L Xu, M Yasuda, X Zhang, P Mitchell & TY Wong (2012): Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care **35**: 556-564.

Figure 1
Flow chart: selection of literature

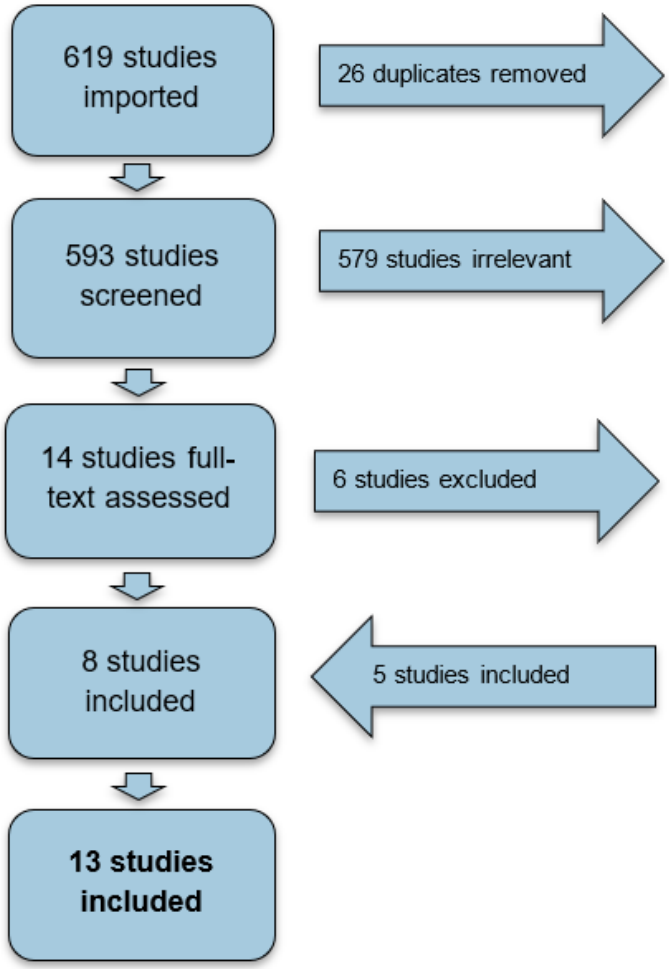

Table 1. Characteristics and results of the included studies

Article	Design	Population	Intervention	Control	Outcome	Results	[95%CI] (p-value)
Shamoon, H (DCCT)	Two in one RCT	Type 1 diabetes	Insulin pump **OR** ≥3 insulin injections/d			*Intensive vs. conventional therapy*	
			Primary prevention (n =348)	Conventional therapy (n=378)	Development of DR: Progression of DR:	Adjusted mean risk: 75% Adjusted mean risk:54 %	[62–85 %] [39-66 %]
			Secondary intervention (n=363)	Conventional therapy (n=352)	Reduced development of PDR or severe NPDR:	Adjusted mean risk: 47%	[14-67 %]
Aiello, L.P. (EDIC)	Follow-up						
Turner, R (UKPDS 33)	RCT	Type 2 diabetes	Insulin (30%) **OR** sulphonylurea (40%) (n=2729)	Conventional therapy (n=1138)	Progression of DR by 2-step in ETDRS	0-3 years: RR: 1.03 0-6 years: RR: 0.83 0-9 years: RR: 0.83 0-12 years: RR: 0.79	99 % CI: [0.79-1.34] (p = 0.78) 99 % CI: [0.67-1.01] (p = 0.017) 99 % CI [0.68-1.00] (p = 0.012) 99 % CI [0.63-1.00] (p = 0.015)
Chaturvedi, N (DIRECT-1)	Two in one RCT	Type 1 diabetes	Prevent 1: Candesartan (n=711) Protect 1: Candesartan (n=951) 32mg/d	Prevent 1: Placebo (n=710) Protect 1: Placebo(n=954)	DR progression based on ≥ 2 or ≥3 steps in ETDRS scale	*Incidence: HR:0.82* *Progression: HR: 1.02*	[0.67;1.00] (p=0.0508) [0.80;1.31] (p=0.85)
Chaturvedi, N (EUCLID)	RCT	Type 1 diabetes	Lisinopril 10mg, dose was increased to 20mg if DBP>75mm Hg at 3 months.	Placebo	Progression of DR by at least one grade from following hierarchy: None, Minimal non-proliferative, Moderate non-proliferative, Severe non-proliferative, Photocoagulated or proliferative	OR: 0.50 aOR: 0.55	[0.28;0.89] (p=0.02) [0.29;1.05] (p=0.07)
Mauer, M (RASS)	RCT	Type 1 diabetes	Enalapril 20mg/d (n=94) **OR** losartan 100mg/d (n=96)	Placebo (n=95)	Progression of DR based on **≥** 2 or **≥**3 steps in ETDRS	*Enalapril vs. c-group:* OR: 0.35 *Losartan vs. c-group:* OR: 0.30	[0.14;0.85] (p=0.02) [0.12; 0.73] (p=0.008)
Sjolie, A.K (DIRECT-2)	RCT	Type 2 diabetes	Candesartan 32mg/d (n=951)	Placebo (n=954)	DR by **≥** 2 or **≥**3 steps in ETDRS scale	*I-group vs C-group* Progression: HR: 0.87 Regression: HR:1.34	[0.70–1.08] (p=0.20) [1.08–1.68] (p=0.009)
Turner, R (UKPDS 38)	RCT	Type 2 diabetes	Captopril (59 mg x 2 /d) (n=400) **OR** atenolol (50 or 100 mg/d) (n=358)	Less tight BP (n=390)	Deterioration of DR by 2-step in ETDRS: Deterioration in VA by 3 lines in ETDRS:	*Tight- vs. less tight BP control* Reduction risk: 34 % Reduction risk: 47 %	99 % CI: [11-50%] (p = 0.0004) 99 % CI: [7-70%] (p = 0.004)
Keech, A.C (FIELD)	RCT	Type 2 diabetes	Fenofibrate 200mg/d (n=4895)	Placebo (n=4900)	Progression of DR based on a 2 step in ETDRS scale	Overall: 9.6 % vs 12.3 % Without DR: 11.4% vs 11.7% Pre-existing DR: 3.1% vs 14.6%	(p=0.19) (p=0.87) (p=0.004)

Beulens, J.W (AdRem)	RCT	Type 2 diabetes	Perindopril indapamide (n=623) **OR** IGC therapy (n=630)	Placebo (n=618) **OR** SGC therapy (n=611)	Progression of DR by ≥1,≥2 and 3 steps ETDRS	*BP- lowering vs placebo*: OR: 0.78 *SGC vs IGC:* OR: 0.84	 [0.57;1.06] (p=0.12) [0.61;1.15] (p=0.27)
Chew, E.Y (ACCORD-EYE)	RCT	Type 2 diabetes	IGC(n=1429) **OR** fenofibrate 160mg + simvastatin (n=806) **OR** BP treatment	SGC (n=1427) **OR** Placebo plus simvastatin (n=787) **OR** standard BP (n=616)	Progression rate of DR: 3 steps in ETDRS scale	*IGC vs SGC*; aOR: 0.67 *IDT vs SDT*; aOR: 0.60 *IBPT vs SBPT:* aOR: 1.23	[0.51;0.87] (p=0.003) [0.42;0.87] (p=0.006) [0.84;1.79] (p=0.29)
Campochiaro, P.A (2004)	RCT	Type 1 and 2 diabetes with DMO	PKC412 50, 100, or 150 mg/d (n=107)	Placebo(n=34)	*Shift in DR classification by ETDRS scale	*In each treatment group:* No shift: 63 % - 73 % Favorable shift: 13 % - 20 % Worsening shift: 7 % - 20 %	 ** ** **
Campochiaro, P.A (2016)	Phase IIa. RCT	DMO	Combination therapy: AKB9778 15mg times 2 daily + ranibizumab 0.3mg/month	Monotherapy AKB9778 15mg times 2 daily + sham **OR** ranibizumab 0.3mg/month + sham	*DRSS 2>step improvement	*Ranibizumab vs AKB 9778:* 4.2% vs 11.4 %	(p=0.149)

*Not primary outcome. **No p-value or 95% CI were given in the study

ACCORD: Action to Control Cardiovascular Risk in Diabetes; AdRem: ADVANCE Retinal Measurement; BP: blood pressure; DBP: diastolic blood pressure; DCCT: Diabetes Control and Complication Trial, DIRECT: DIabetic REtinopathy Candesartan Trials; DMO: diabetes macular oedema; DR: diabetes retinopathy; DRSS: Diabetic Retinopathy Severity Scale; EDIC: Epidemiology of Diabetes Interventions and Complications; ETDRS: Early Treatment Diabetic Retinopathy Study; FIELD: The Fenofibrate Intervention and Event Lowering in Diabetes; IBPT: intensive blood pressure therapy; IDT: intensive dyslipidemia theray; IGC: intensive glucose control; OCT: optical coherence tomography; RCT: randomized clinical trial; SBPT: standard blood pressure therapy; SDT: standard dyslipidemia therapy; SGC: standard glucose control; UKPDS: United Kingdom Prospective Diabetes Study.

Table 2. Cochrane Risk of Bias Tool for Randomized Controlled Trials used to assess the studies

Articles	Random sequence	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personelle	Blinding of outcome	Handling of incomplete data	Conclusion
Shamoon, F (DCCT)	Unclear	Low	Low	Unclear	Low	Low	Low	Fair quality
Aiello, L.P (EDIC)*	Unclear	Low	Low	Unclear	Low	Low	Low	Fair quality
Turner, R (UKPDS 33)	Low	Low	Unclear	Unclear	Low	Low	Low	Fair quality
Chaturvedi, N (DIRECT-1)	Low	Low	Low	Unclear	Low	Low	Low	Good quality
Chaturvedi, N (Euclid)	Low	Low	Unclear	Unclear	Low	Low	Low	Fair quality
Mauer,M (RASS)	Low	Low	Low	Unclear	Low	Low	Low	Good quality
Sjolje, A.K (DIRECT-2)	Low	Low	Low	Unclear	Low	Low	Low	Good quality
Turner, R (UKPDS 38)	Low	Low	Unclear	Unclear	Low	Low	Low	Fair quality
Keech, A.C (FIELD)	Low	Unclear	Low	Unclear	Low	Low	Low	Fair quality
Beulens (AdRem)	Low	Low	Low	Unclear	Low	Low	Low	Good quality
Chew, E.Y (ACCORD-EYE)	Low	Unclear	Low	Unclear	Low	Low	Low	Fair quality
Campochiaro, P.A (2004)	Low	Low	Unclear	Unclear	Low	Low	Low	Fair quality
Campochiaro, P.A. (2016)	Low	Low	Unclear	Unclear	Low	Low	Low	Fair quality

*The EDIC study was based on DCCT, and we have used the same tool to judge the quality of this article to make the articles comparable although the former is an observational study.

ACCORD: Action to Control Cardiovascular Risk in Diabetes; AdRem: ADVANCE Retinal Measurement; DCCT: Diabetes Control and Complication Trial; DIRECT: DIabetic REtinopathy Candesartan Trials; EDIC: Epidemiology of Diabetes Interventions and Complications; FIELD: The Fenofibrate Intervention and Event Lowering in Diabetes; UKPDS: United Kingdom Prospective Diabetes Study.