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[Prognosis Protocol]

Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

Primary objectives

To assess prognostic factors for predicting the occurrence of PDR in individuals with diabetic retinopathy.

Table 1. PICOTS of the primary objective

Population	Male and female adults ≥ 18 years of age of any ethnicity with DR (NPDR), diagnosed as per standard clinical protocol
Index prognostic factors	<p>Broad review of prognostic factors associated with the development of PDR.</p> <p>Specific prognostic factors of interest will include, but not be restricted to, routinely collected patient demographics and information, such as age, gender, ethnicity, socio-economic status, and smoking habits; frequently obtained standard clinical data, such as comorbidities (presence/absence of cardiovascular disease, cerebrovascular disease, nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m²), peripheral neuropathy and specifically foot ulcers, amputation), body mass index (BMI), neck/waist circumference, glycated haemoglobin, blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, and functional and structural retinal biomarkers in the prognostic context of the development and progression of PDR. Prognostic factors will be considered in the absence of treatment for DR.</p> <p>It is expected that prognostic factors will generally be measured at the time participants enter the study, and indeed after the diagnosis of DR. If measures of prognostic factors are available at other</p>

time points, and these coincide in more than one study, we may consider investigating them, additionally, at other time points.

Studies evaluating risk factors requiring invasive procedures to be measured (e.g. aqueous or vitreous samples to measure growth factors in these fluids) not performed in routine clinical practice will be excluded.

Comparator	Not applicable
Outcomes	Progression from DR (NPDR) to any stage of PDR. Participants who have received laser PRP for the treatment of PDR will be considered to have progressed to the outcome of PDR.
Timing	3 years (\pm 2 years), 8 years (\pm 2 years), or lifelong, if available. If not, other time points will be accepted and presented. PDR can occur very rapidly - in days - or take months or years to develop. We will also determine over what time period the outcomes are predicted by the risk factors investigated.
Setting	Any clinical setting. No geographical limitations

Secondary objectives

To assess prognostic risk factors for predicting the progression of PDR from less than HRC-PDR to HRC-PDR.

Table 2. PICOTS of the secondary objective

Population	Male and female adults \geq 18 years of age of any ethnicity with less than HRC-PDR, diagnosed as per standard clinical protocol
Index prognostic factors	<p>We anticipate that less information will be available regarding prognostic factors associated with progression from PDR to HRC-PDR. Prognostic factors of interest will include, but not be restricted to, routinely collected patient demographics and information, such as age, gender, ethnicity, socio-economics, and smoking habits; frequently obtained standard clinical data, such as comorbidities (presence/absence of cardiovascular disease, cerebrovascular disease, nephropathy and specifically chronic kidney failure (defined as estimated GFR of < 60 mL/min/1.73 m²), peripheral neuropathy and specifically foot ulcers, amputation), BMI, neck/waist circumference, glycat- ed haemoglobin, blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, and functional and structural retinal biomarkers in the prognostic context of the development and progression of HRC-PDR. The scope of this review will not extend to the evaluation of the effect of treatment on progression to HRC-PDR, and as such, prognostic factors will be considered in the absence of previous treatment for PDR.</p> <p>It is expected that prognostic factors will generally be measured at the time participants enter the study, and indeed after the diagnosis of less than HRC-PDR. If measures of prognostic factors are available at other time points, and these coincide in more than one study, we may consider investi- gating them additionally at other time points. Prognostic factors requiring invasive procedures to be measured (e.g. aqueous or vitreous samples to measure growth factors in these fluids) not per- formed in routine clinical practice will not be considered.</p>
Comparator	Not applicable
Outcomes	Progression from PDR to HRC-PDR. Participants who received laser PRP for the treatment of PDR will be considered to have progressed to the outcome of PDR.
Timing	<p>3 years (\pm 2 years), 8 years (\pm 2 years), or lifelong, if available. If not, other time points may be con- sidered and presented.</p> <p>PDR can occur very rapidly - in days - or take months or years to develop. We will also determine over what time period the outcomes are predicted by the risk factors investigated.</p>

SettingAny clinical setting. No geographical limitations

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity relating to two key areas.

1. Clinical heterogeneity including the effect of different comorbidities, medications, and interventions in study cohorts. Differences in how outcomes are measured, such as diagnoses of PDR (clinical examination versus supported by imaging/imaging technologies used) and how progression is defined.
2. Methodological heterogeneity generated from different study designs, and how robustly studies are conducted with regard to risk of bias and approach to analysis.

We will explore the effects of these aspects of heterogeneity if a meta-analysis is conducted.

BACKGROUND

Description of the health condition and context

Health condition

Diabetes mellitus (DM) is a chronic metabolic disease characterised by elevated blood glucose levels which, over time, lead to multiorgan dysfunction. The global prevalence of diabetes is estimated to be 9.3% (463 million) and is expected to escalate to 10.2% (578 million) by 2030 due to population expansion and ageing, urbanisation, increasing levels of obesity, inadequate nutrition, and sedentary lifestyles (Saeedi 2019). Diabetic retinopathy (DR) occurs because of neurovascular degeneration triggered by hyperglycaemia, and is the most common microvascular complication of diabetes. Worldwide prevalence of retinopathy related to diabetes has recently been determined to be 27% between the period of 2015 and 2019 (Thomas 2019).

DR is a progressive condition with advancing levels of severity. Simplified systems based on the Early Treatment Diabetic Retinopathy Study (ETDRS) have been devised to classify stages of DR based on the presence of various microvascular lesions. DR can be categorised into two main stages: non-proliferative (NPDR), and the more serious, sight-threatening, proliferative stage (PDR) (Stitt 2016). The earliest visible clinical signs of NPDR are microaneurysms which represent damage to retinal capillaries. Mild NPDR is defined by the presence of at least one retinal microaneurysm or haemorrhage. As disease severity progresses to moderate and severe NPDR, the number of microaneurysms and haemorrhages increase, and exudates, cotton-wool spots, venous beading, and intraretinal vascular abnormalities develop, signifying increasing capillary hyperpermeability and non-perfusion. Severe NPDR is defined by the '4:2:1 rule', which is the presence of intraretinal microvascular abnormality (IRMA) in all four quadrants, venous beading in at least two quadrants, or IRMA in at least one quadrant.

Retinal ischaemia (also referred to as retinal capillary non-perfusion) is considered to be the main catalyst for the occurrence of PDR. PDR is characterised by the development of abnormal new blood vessels (so-called new vessels), with or without accompanying fibrous tissue (i.e. fibromuscular membranes), at the optic disc (new vessels in the disc (NVD)) or elsewhere in the retina (new vessels elsewhere (NVE)). The ischaemic retina triggers the release of growth factors, including vascular endothelial growth factor (VEGF), which promote the growth of these new vessels in a futile attempt to restore vascular supply to the retina. However, new vessels are fragile and often rupture leading to haemorrhages inside the eye (so-called vitreous haemorrhages). PDR can progress in severity from mild to high-risk characteristics (HRC-PDR). The latter is defined by the presence of NVD > 1/4 to 1/3 disc area in size or NVD/NVE associated with bleeding, in the form of vitreous or pre-retinal haemorrhages (Diabetic Retinopathy Study Research Group 1991). In severe cases, PDR can lead to complete visual loss resulting from proliferation of fibrovascular membranes and retinal detachment.

Almost all, if not all, individuals with DM will develop DR if they live for a sufficient period of time. During the first two decades of disease, nearly all people with type 1 diabetes (T1D) and 60% of those with type 2 diabetes (T2D) develop DR (Fong 2003). A

pooled analysis to determine the global prevalence of DR found that over one-third of individuals with DM had DR and, of these, approximately 7%, equating to 17 million individuals (Yau 2012). A more recent pooled analysis estimated the global prevalence of PDR to be 1.4% for the period of 2015 to 2019 (Thomas 2019). However, it acknowledged significant heterogeneity in study populations and methodology as limiting factors in accurately deriving the global prevalence of DR.

Treatment

The International Diabetes Federation advises regular eye examinations every one to two years for people with diabetes and no retinopathy. Once DR develops, the frequency of assessments should be increased depending on the severity of the retinopathy and level of control of systemic factors (Fred Hollows Foundation 2015). Currently, treatment options for NPDR are lacking, and treatment is only given when PDR or diabetic macular oedema (DMO) ensue.

The Diabetic Retinopathy Study (DRS) demonstrated that risk of severe visual loss in people with HRC-PDR was reduced by 50% at two and five years with panretinal laser photocoagulation (PRP) treatment (Diabetic Retinopathy Study Research Group 1987). A Cochrane intervention review also verified that PRP is beneficial in reducing vision loss and progression in PDR (Evans 2014). PRP involves burning the retina, avoiding the macula (the area responsible for the central sight), with spots of laser, leading to regression of new vessels following treatment. The exact mechanism of action of PRP remains unclear, but it is presumably due to the reduced oxygen requirement of the less extensive viable retina post-treatment, and diminished growth factor production resulting from ablation of the ischaemic retina (Doft 1984). PRP generally preserves rather than improves vision and may be associated with adverse side effects such as diminished peripheral vision, night vision, or both, and exacerbation of DMO.

The advent of intravitreal anti-VEGF injections has become a pharmacological alternative to PRP (Cheung 2010). A Cochrane intervention review published in 2014 determined that evidence from randomised controlled trials (RCTs) for the efficacy and safety of anti-VEGF drugs in the treatment of PDR was of low quality, but did find a reduction in the risk of intraocular bleeding (Martinez-Zapata 2014). More recent RCTs have shown that anti-VEGFs are non-inferior to PRP in the treatment of PDR (Gross 2015; Sivaprasad 2017). However, the great majority of participants included in these RCTs did not have HRC-PDR. A recent retrospective review determined that people with PDR who are treated with anti-VEGF therapy alone and subsequently become lost to follow-up are more susceptible to developing irreversible blindness (Wubben 2019). Furthermore, anti-VEGFs do not appear to be cost-effective unless they are used to treat concomitant DMO and PDR (Hutton 2017). Given that several long-term studies have verified that the beneficial effects of PRP generally last indefinitely (Chew 2003; Dogru 1999), PRP thus remains the mainstay therapy for PDR. Even with treatment, however, progression of PDR and the development of further complications may still occur in severe cases.

Moment of prognostication

The moment of prognostication is any time after an individual has been diagnosed as having diabetes and DR, and prior to the occurrence of PDR.

Clinical context

Although many people develop DR, few will progress to the stage of PDR. However, all individuals with DR require lifelong follow-up, and Diabetic Eye Screening Services and Eye Health Services are currently finding it impossible to contend with the demand. A concerning report revealed that lack of capacity within hospital eye services resulted in permanent sight loss in patients of all ages due to delayed appointments (Foot 2017). The Liverpool Risk Calculation Engine study group determined that implementing individualised screening intervals based on standard clinical data would facilitate more effective management of resources into targeting high-risk groups (Eleuteri 2017). Identifying prognostic factors signalling risk of visual loss would thus be extremely beneficial in the enhancement and development of predictive models to optimise resources.

Description of the prognostic/predictive model(s)/factor(s)

This systematic review will focus on identifying prognostic factors for progression to PDR and to HRC-PDR. Information on some of the risk factors entertained is provided below.

Diabetes duration appears to be a key predictor of the development and progression of DR, independent of glycaemic control (Fong 2003). For example, in individuals with T1D, PDR is not usually observed for the first 10 years of disease, but there is a rapid increase in incidence, to approximately 60%, by 20 years of disease duration (Klein 2008).

The Diabetes Control and Complications Trial (DCCT) provided evidence that rigorous glycaemic control delays development and progression of DR in T1D (Diabetes Control and Complications Group 1998). Similarly, the UK Prospective Diabetes Studies (UKPDS) (Turner 1998) was pivotal in establishing the beneficial effect of regulating glycaemic levels in people with T2D. A meta-analysis of 16 RCTs found that the risk of retinopathy progression was lower after two years of intensive glucose control. However, it concluded that progression to and within NPDR is clinically different from progression to PDR, but not all studies separate these stages. In those that did, long-term intensive glucose control significantly reduced retinopathy progression to PDR (odds ratio 0.44 (95% confidence interval (CI) 0.22 to 0.87), $P = 0.018$; test for heterogeneity, $P = 0.991$) (Wang 1993).

A Cochrane Review assessed the effects of intensive versus conventional glycaemic control on long-term diabetic complications in people with T1D, and aimed to determine whether near normo-glycaemic values are beneficial. The review confirmed that tight blood sugar control significantly reduces the risk of developing retinopathy (23/371 (6.2%) versus 92/397 (23.2%); risk ratio 0.27 (95% CI 0.18 to 0.42); $P < 0.001$; 768 participants; 2 trials; high-quality evidence). However, the beneficial effect of tight blood sugar control seems to become weaker once retinopathy is present (Fullerton 2014). A recent review consisting of five RCTs with large sample sizes and long-term follow-up found that in people with worse-than-moderate NPDR, intensive glycaemic control may not confer any benefits in terms of progression (Liu 2020).

International evidence-based clinical practice guidelines recognise the benefit of glycaemic control (Fred Hollows Foundation 2015). However, current management approaches do not fully

prevent progression to PDR, and there is no glycaemic threshold below which protection is certain (Diabetes Control and Complications Group 1993).

The current evidence on the effect of hypertension on progression to and within PDR seems unclear. Although, the Wisconsin Epidemiological Study of Diabetic Retinopathy (Klein 1998), determined hypertension to be associated with progression to PDR in people with T1D and the UKPDS, Turner 1998, identified a corresponding relationship in those with T2D, other studies failed to corroborate these findings. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study, intensive blood pressure control did not have a significant effect on retinopathy progression (Chew 2014). A Cochrane Review of 15 RCTs including participants with T1D and T2D conducted mainly in North America and Europe determined an association between reduced blood pressure and prevention of DR for up to four to five years (Do 2015). However, the review concluded that the available evidence did not support a benefit of intervention on blood pressure on progression to PDR or moderate/severe visual loss after five years of follow-up. A recent meta-analysis similarly concluded that intensive blood pressure control reduced relative risk of incidence of DR by 17% in T2D (Zhou 2018a). However, the available data were insufficient to confirm a relative risk reduction for DR progression or incidence of PDR.

The effect of cholesterol on the progression of DR also remains uncertain. The Collaborative Atorvastatin Diabetes Study found no difference in the progression of DR between participants randomised to receive a daily dose of atorvastatin and those randomised to placebo (Colhoun 2004). Investigation of fibrates in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found a significant relative reduction in the need for PRP in T2D patients treated with a fibrate, but a reduction in DR progression was observed only in those with retinopathy at baseline (Keech 2007). However, it is acknowledged that fenofibrate may benefit the retina independently of its lipid-lowering effects (revised by Stewart and Lois) (Stewart 2018). An ongoing Cochrane Review with a published protocol will evaluate the evidence in this regard (Inoue 2019).

A recent systematic review and meta-analysis of observational studies exploring associations between serum lipids and the occurrence of DR found a slightly higher low-density lipoprotein cholesterol in cases with DR (Zhou 2018b). The review identified that in a large population-based, longitudinal, observational study of people with pre-existing DR at baseline, poor control of total cholesterol was associated with a higher incidence of sight-threatening retinopathy after adjusting for potential confounders. Poor control of triglycerides was also associated with progression to PDR, and this was greater when all lipid types were abnormal (Srinivasan 2017). There is currently no Cochrane Review evaluating the relationship between cholesterol and DR. Although definitive evidence is lacking regarding the effect of optimal control of blood lipids on reducing the incidence and progression of DR, it is advisable in terms of benefits to overall health.

Diabetes duration, hyperglycaemia, hypertension, and hyperlipidaemia, whilst likely relevant for determining the risk of DR development (i.e. from no DR to presence of DR), may not fully explain the highly variable progression of NPDR to PDR, as also pointed out in a recent review by Sivaprasad and colleagues (Sivaprasad 2019). Many studies have assessed

generalised DR progression using data from screening programmes where the majority of people included had no DR or only mild NPDR. To our knowledge, there are currently no systematic reviews on prognostic factors for the development of PDR and its progression.

This review aims to identify factors conferring increased risk of PDR and HRC-PDR in people with diabetes once retinopathy is present.

Health outcomes

This review will consider the prognostic factors associated with the development of PDR and progression from less than HRC-PDR to HRC-PDR. PDR and HRC-PDR are thus the health outcomes to be investigated.

As stated above, PDR is diagnosed by the presence of NVD on or within 1-disc diameter, or NVE. HRC-PDR is defined according to the ETDRS as NVD > 1/4 to 1/3 disc area, NVD of any extent, or NVE if associated with the presence of vitreous haemorrhage or pre-retinal haemorrhage.

Alarming, many people with diabetes can progress to the sight-threatening stage of PDR without developing any obvious prior warning symptoms. The DRS found that approximately 50% of people with PDR who do not receive timely treatment will become legally blind within five years ([Diabetic Retinopathy Study Research Group 1981](#)). The ETDRS was important in establishing that PRP treatment can be deferred in patients with NPDR or PDR until high-risk characteristics develop ([Diabetic Retinopathy Study Research Group 1991](#)). The study also identified that only 50% of eyes assigned to deferral of treatment (until HRC-PDR ensued) progressed to HRC-PDR after seven years of follow-up.

A large cohort study of 7.7 million patients contributing to the Clinical Practice Research Datalink evaluated population trends in the 10-year incidence and prevalence of DR in the UK from 2004 to 2014, by diabetes type, age, sex, ethnicity, deprivation, region, and calendar year ([Mathur 2017](#)). The study found that the age-standardised prevalence of DR decreased over time from 2.6% to 2.2%, whilst the age-standardised prevalence of severe DR remained stable at 0.1%. The incidence also remained stable at one event per 10,000 person-years ([Mathur 2017](#)). This suggests that despite improved medical management of DM, the threat of PDR and its complications remain a significant problem.

The time horizon for the evaluation of health outcomes in this review will be 3 years (± 2 years), 8 years (± 2 years), or lifelong, if available. If not, other time points will be acceptable and presented.

Why it is important to do this review

We are undertaking this review to gather evidence on prognostic factors for the development and progression of PDR. This information is essential for ophthalmologists and other healthcare professionals for the counselling and management of people with diabetes and thus for patients and their families. Our findings will help clinicians to provide advice to their patients regarding modifiable risk factors, to determine in a more personalised manner the interval required for the purpose of monitoring their disease, and to consider early intervention in high-risk groups. Due to the increasing prevalence of diabetes and the limited resources of healthcare systems, tailoring health care in an individualised manner seems essential, avoiding the need to review patients in low-risk groups too often and guaranteeing prompt and close evaluation of those who are at high risk.

This prognostic review may help to identify targets for new interventions that aim to modify the course of the disease. Furthermore, the findings may guide the design and analysis of future interventional clinical trials, and will highlight areas where further research is required.

To our knowledge, there are currently no systematic reviews on prognostic factors specifically for the development of PDR and its progression to high-risk PDR. A systematic review on prognostic prediction models for DR progression was published recently ([Haider 2019](#)). The aim of this review was to summarise the performance of existing models in predicting progression of retinopathy and their applicability for higher-risk DR patients under hospital care to predict the need for treatment or loss of vision. Based on their findings, the authors identified the need for an accurate model that can determine patients' individual risk of progression to treatment stage or loss of vision. They determined that this knowledge will allow for a more appropriate use of resources and further optimisation of services, especially for individuals with a higher risk of progression ([Haider 2019](#)). This Cochrane Review will provide evidence-based information on risk factors for the development and progression of PDR that can be used for the development of future prognostic models.

OBJECTIVES

Primary objectives

To assess prognostic factors for predicting the occurrence of PDR in individuals with diabetic retinopathy.

Table 1. PICOTS of the primary objective

Population	Male and female adults ≥ 18 years of age of any ethnicity with DR (NPDR), diagnosed as per standard clinical protocol
Index prognostic factors	<p>Broad review of prognostic factors associated with the development of PDR.</p> <p>Specific prognostic factors of interest will include, but not be restricted to, routinely collected patient demographics and information, such as age, gender, ethnicity, socio-economic status, and smoking habits; frequently obtained standard clinical data, such as comorbidities (presence/absence of cardiovascular disease, cerebrovascular disease, nephropathy and specifically chronic kidney failure (defined as estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m²), peripheral neuropathy and specifically foot ulcers, amputation), body mass index (BMI), neck/waist circumference, glycated haemoglobin, blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, and functional and structural retinal biomarkers in the prognostic con-</p>

text of the development and progression of PDR. Prognostic factors will be considered in the absence of treatment for DR.

It is expected that prognostic factors will generally be measured at the time participants enter the study, and indeed after the diagnosis of DR. If measures of prognostic factors are available at other time points, and these coincide in more than one study, we may consider investigating them, additionally, at other time points.

Studies evaluating risk factors requiring invasive procedures to be measured (e.g. aqueous or vitreous samples to measure growth factors in these fluids) not performed in routine clinical practice will be excluded.

Comparator	Not applicable
Outcomes	Progression from DR (NPDR) to any stage of PDR. Participants who have received laser PRP for the treatment of PDR will be considered to have progressed to the outcome of PDR.
Timing	3 years (\pm 2 years), 8 years (\pm 2 years), or lifelong, if available. If not, other time points will be accepted and presented. PDR can occur very rapidly - in days - or take months or years to develop. We will also determine over what time period the outcomes are predicted by the risk factors investigated.
Setting	Any clinical setting. No geographical limitations

Secondary objectives

Table 2. PICOTS of the secondary objective

To assess prognostic risk factors for predicting the progression of PDR from less than HRC-PDR to HRC-PDR.

Population	Male and female adults \geq 18 years of age of any ethnicity with less than HRC-PDR, diagnosed as per standard clinical protocol
Index prognostic factors	<p>We anticipate that less information will be available regarding prognostic factors associated with progression from PDR to HRC-PDR. Prognostic factors of interest will include, but not be restricted to, routinely collected patient demographics and information, such as age, gender, ethnicity, socio-economics, and smoking habits; frequently obtained standard clinical data, such as comorbidities (presence/absence of cardiovascular disease, cerebrovascular disease, nephropathy and specifically chronic kidney failure (defined as estimated GFR of < 60 mL/min/1.73 m²), peripheral neuropathy and specifically foot ulcers, amputation), BMI, neck/waist circumference, glycat- ed haemoglobin, blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, and functional and structural retinal biomarkers in the prognostic context of the development and progression of HRC-PDR. The scope of this review will not extend to the evaluation of the effect of treatment on progression to HRC-PDR, and as such, prognostic factors will be considered in the absence of previous treatment for PDR.</p> <p>It is expected that prognostic factors will generally be measured at the time participants enter the study, and indeed after the diagnosis of less than HRC-PDR. If measures of prognostic factors are available at other time points, and these coincide in more than one study, we may consider investi- gating them additionally at other time points. Prognostic factors requiring invasive procedures to be measured (e.g. aqueous or vitreous samples to measure growth factors in these fluids) not per- formed in routine clinical practice will not be considered.</p>
Comparator	Not applicable
Outcomes	Progression from PDR to HRC-PDR. Participants who received laser PRP for the treatment of PDR will be considered to have progressed to the outcome of PDR.
Timing	3 years (\pm 2 years), 8 years (\pm 2 years), or lifelong, if available. If not, other time points may be con- sidered and presented.

PDR can occur very rapidly - in days - or take months or years to develop. We will also determine over what time period the outcomes are predicted by the risk factors investigated.

Setting

Any clinical setting. No geographical limitations

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity relating to two key areas.

1. Clinical heterogeneity including the effect of different comorbidities, medications, and interventions in study cohorts. Differences in how outcomes are measured, such as diagnoses of PDR (clinical examination versus supported by imaging/imaging technologies used) and how progression is defined.
2. Methodological heterogeneity generated from different study designs, and how robustly studies are conducted with regard to risk of bias and approach to analysis.

We will explore the effects of these aspects of heterogeneity if a meta-analysis is conducted.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Eligible study designs will include prospective or retrospective cohort and case-control longitudinal studies involving patients who have not had previous treatment for DR; as well as randomised controlled trials (RCTs) evaluating therapeutic interventions to prevent the progression of DR where there is a control, untreated arm. We will also include studies based on longitudinal registry data. It is a mandatory requirement that relevant studies must evaluate prognostic factors involved specifically in the development and progression of PDR, as opposed to generalised progression of retinopathy.

Studies investigating general microvascular complications of diabetes but including a subset of data related to factors involved in the development of PDR will be eligible for inclusion, if information on this group (PDR) is specifically given.

Exclusion criteria

We will exclude case reports, as they will introduce selection bias, and editorials/letters to editor not containing primary data. We will not include cross-sectional studies, as this is a less appropriate study design for the evaluation of prognostic factors for the development or progression of disease.

Targeted population

The target population will consist of adults (≥ 18 years of age) of any gender with NPDR or PDR with less than HRC-PDR, diagnosed as per standard clinical practice. Studies involving participants of all ethnicities, geographical locations, and socio-economic status will be eligible for inclusion. Any appropriate studies including a subset

of relevant participants will be considered as potentially eligible if data from this subset are given separately.

Types of prognostic/predictive factor(s) or model(s)

This review will consider prognostic factor studies only. Specific prognostic factors of interest will include, but are not restricted to, routinely collected patient demographics and information, such as age, gender, ethnicity, socio-economic status, and smoking habits; frequently obtained standard clinical data, such as comorbidities (presence/absence of cardiovascular disease, cerebrovascular disease, nephropathy and specifically chronic kidney failure (defined as estimated GFR of < 60 mL/min/1.73 m²), peripheral neuropathy and specifically foot ulcers, amputation), BMI, neck/waist circumference, glycated haemoglobin, blood pressure, low-density lipoprotein, high-density lipoprotein, triglycerides, and functional and structural retinal biomarkers in the prognostic context of the development and progression of PDR.

We will exclude studies evaluating prognostic factors involving invasive procedures that cannot be practically undertaken in a clinical setting (such as aqueous/vitreous sampling) and are thus unlikely to be translatable to routine clinical practice.

It is expected that prognostic factors will generally be measured at the time participants enter the study, and indeed after the diagnosis of DR or PDR. If measures of prognostic factors are available at other time points, and these coincide in more than one study, we may consider investigating them additionally at other time points.

Types of outcomes to be predicted

Development of PDR

The development of PDR will be determined by the presence of retinal new vessels, either at the disc (NVD) or elsewhere in the retina (NVE) as determined by fundus examination, fundus photography, or fundus fluorescein angiography. We will consider participants requiring laser treatment for PDR specifically to have progressed to the outcome of PDR.

Development of HRC-PDR

Progression from less than HRC-PDR to HRC-PDR. HRC-PDR is defined according to the ETDRS as: i) NVD $> 1/4$ to $1/3$ disc area; ii) NVD of any extent or NVE if associated with the presence of vitreous haemorrhage or pre-retinal haemorrhage. These features may be assessed by clinical examination or by the grading of ophthalmic images, both fundus photography and fundus fluorescein angiograms. Participants requiring laser treatment for HRC-PDR specifically will be considered as having progressed to the outcome of HRC-PDR.

The time horizon for the evaluation of health outcomes in this review will be 3 years (± 2 year), 8 years (± 2 years), or lifelong, if available. If not, other time points will be accepted and presented.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases. A search has been developed around the following components, “prognostic factors”, “proliferative diabetic retinopathy”, and “development and progression”. There will be no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library ([Appendix 1](#)).
- MEDLINE Ovid (1946 to present) ([Appendix 2](#)).
- Embase Ovid (1980 to present) ([Appendix 3](#)).

Searching other sources

We will supplement the search by screening the reference lists of eligible articles. We will not include grey literature sources in the review, as we do not expect these to be sufficiently informative to justify the extra resources required in conducting the searches.

Data collection

Selection of studies

Two review authors, independently and masked to each other's initial decisions, will review titles and abstracts of studies identified by the electronic searches and classify them as potentially eligible or ineligible. We will use online review management software for this purpose ([Covidence](#)). Any discrepancies will be resolved by discussion or by consultation with a third review author if necessary. We will obtain the full-text articles of potentially eligible studies, and two review authors will independently classify them as included or excluded. Any discrepancies will be resolved by discussion or by consultation with a third review author if necessary. We will report the selection process of studies in a PRISMA flow diagram and document reasons for exclusion of the studies excluded after full-text review.

Data extraction and management

To account for heterogeneity amongst studies, data extraction will involve two stages. The first stage will consist of a mapping exercise to categorise eligible studies according to their design, prognostic factors evaluated, time points of prognostic factor measurements and outcomes, and type of analysis/effect estimates. We will enter information into a pilot-tested spreadsheet specifically designed for this purpose.

In the second stage, we will extract data for each prognostic factor of interest from relevant studies which have been identified by stage one as having common factors appropriate for meta-analysis.

Two review authors will independently undertake data extraction. Any disagreements will be resolved by discussion or with the involvement of a third review author if necessary. We will use the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS-PF) to guide data extraction ([Appendix 4](#)).

We will extract and enter the following data, if available, according to the following categories.

- Study
 - * Title
 - * Authors' contact details
 - * Sources of funding
 - * Dates
- Study design
 - * Prospective or retrospective cohort or case-control studies, RCTs evaluating therapeutic interventions to prevent progression of DR where there is a control, untreated arm, and longitudinal registry data
- Participants
 - * Eligibility criteria and recruitment method
 - * Participant description
 - * Details of treatments received, if relevant
- Outcomes to be predicted
 - * Definition and method of measurement of outcomes
 - * Types of outcomes: 1) developing PDR; 2) progressing from less than HRC-PDR to HRC-PDR
 - * Time of outcome occurrence
- Prognostic factors
 - * Number and type of prognostic factors
 - * Definition and method for measurement
 - * Timing of prognostic factor measurement
- Sample size
 - * Sample size calculation
 - * Number of participants and number of outcomes
 - * Outcomes per variable
- Missing data
- Analysis
 - * Modelling method
- Results
 - * Unadjusted and adjusted prognostic effect estimates (e.g. risk ratio, odds ratio, hazard ratio, or mean difference) for each prognostic factor of interest and corresponding measure of uncertainty (e.g. standard errors, variances, or confidence intervals)
 - * For each extracted adjusted prognostic effect estimate of interest, the set of adjusted factors

Assessment of risk of bias in included studies

We will use the Quality in Prognosis Studies (QUIPS) tool to assess risk of bias of the included studies ([Appendix 5](#)) ([Hayden 2013](#)). We will consider the following domains for each eligible study.

1. Study participation: is the study sample representative of the population of interest?
2. Study attrition: is the sample data available representative of the study sample?
3. Prognostic factor measurement: is the prognostic factor of interest measured in a similar way for all participants?
4. Outcome measurement: is the outcome of interest measured in a similar way for all participants?
5. Adjustment for other prognostic factors: are potentially confounding factors appropriately accounted for?
6. Statistical analysis and reporting: is the statistical analysis appropriate, and are all primary outcomes reported?

Two review authors will independently assess risk of bias, with any discrepancies arbitrated by a third review author.

We will assess each 'Risk of bias' domain as low, moderate, or high, and detail our reasoning for such assessments.

Measures of association or predictive performance measures to be extracted

For each factor of interest, we will extract estimates of prognostic effect such as hazard ratios, risk ratios, odds ratios, or mean differences with a measure of their uncertainty (standard errors, variances, or confidence intervals). We will collect adjusted prognostic effect estimates preferentially, and document the set of adjustment factors used.

Dealing with missing data

We will contact study authors if further information or clarification is required. When time-to-event analyses were performed, and adjusted hazard ratio estimates and their uncertainty are unavailable, if the summary statistics reported permit, we will attempt to derive unadjusted estimates and their standard errors following guidance described by Tierney and colleagues ([Tierney 2007](#)).

Assessment of heterogeneity

We anticipate there will be statistical heterogeneity due to clinical and methodological differences between studies. Since the I^2 statistic can be problematic in certain situations ([Rücker 2008](#)), we will quantify heterogeneity using τ^2 . Where there is an appropriate number of studies included in a meta-analysis, we will also present 95% prediction intervals.

Assessment of reporting deficiencies

We will assess small-study effects using contour-enhanced funnel plots when 10 or more studies are included in a meta-analysis. We anticipate variation in effect measures, length of follow-up, etc., and therefore expect to include few studies in each meta-analysis. Consequently, we do not plan to perform funnel plot asymmetry tests given the low power of such tests when studies are few ([Debray 2018](#)).

Data synthesis

Data synthesis and meta-analysis approaches

We will conduct meta-analysis (i.e. report a weighted average of the individual study measures of association) in clinically relevant groups using a random-effects approach. We will stratify by different time points of outcomes and meta-analyse hazard ratios, odds ratios, and risk ratios separately for each prognostic factor and outcome. Similarly, unadjusted and adjusted associations will be reported separately. Our primary analyses will focus on adjusted estimates. If we determine that conducting a meta-analysis is inappropriate due to heterogeneity, we will present a narrative or tabulated summary. We will use 95% confidence intervals throughout.

Sensitivity analysis

We will perform sensitivity analyses to explore the impact of the following factors (when applicable) on effect sizes by excluding:

- studies at high risk of bias in one or more domains;
- retrospective studies.

Conclusions and 'Summary of findings'

We will prepare a 'Summary of findings' table assessing the certainty of the evidence using GRADE modified for prognostic factor studies ([Foroutan 2020](#)). We will use the table to clearly identify factors that influence the development of PDR and progression to HRC-PDR and our confidence in the estimates of effect.

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REFERENCES

Additional references

Cheung 2010

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;**376**(9735):124-36.

Chew 2003

Chew EY, Ferris FL 3rd, Csaky KG, Murphy RP, Agrón E, Thompson Darby JS, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology* 2003;**110**(9):1683-9.

Chew 2014

Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, Greven C, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology* 2014;**121**(12):2443-51.

Colhoun 2004

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**(9435):685-96.

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 2 September 2020. Melbourne: Veritas Health Innovation. Available at www.covidence.org.

Debray 2018

Debray TP, Moons KG, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: a comparison of new and existing tests. *Research Synthesis Methods* 2018;**9**(1):41-50.

Diabetes Control and Complications Group 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* 1993;**329**(14):977-86.

Diabetes Control and Complications Group 1998

The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Archives of Ophthalmology* 1998;**116**(7):874-86.

Diabetic Retinopathy Study Research Group 1981

Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. *Ophthalmology* 1981;**88**(7):583-600.

Diabetic Retinopathy Study Research Group 1987

Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. *International Ophthalmology Clinics* 1987;**27**(4):239-53.

Diabetic Retinopathy Study Research Group 1991

Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology* 1991;**98**(5):766-85.

Do 2015

Do DV, Wang X, Vedula SS, Marrone M, Sleilati G, Hawkins BS, et al. Blood pressure control for diabetic retinopathy. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No: CD006127. [DOI: [10.1002/14651858.CD006127.pub2](https://doi.org/10.1002/14651858.CD006127.pub2)]

Doft 1984

Doft BH, Blankenship G. Retinopathy risk factor regression after laser panretinal photocoagulation for proliferative diabetic retinopathy. *Ophthalmology* 1984;**91**(12):1453-7.

Dogru 1999

Dogru M, Nakamura M, Inoue M, Yamamoto M. Long-term visual outcome in proliferative diabetic retinopathy patients after panretinal photocoagulation. *Japanese Journal of Ophthalmology* 1999;**43**(3):217-24.

Eleuteri 2017

Eleuteri A, Fisher AC, Broadbent DM, García-Fiñana M, Cheyne CP, Wang A, et al. Individualised variable-interval risk-based screening for sight-threatening diabetic retinopathy: the Liverpool Risk Calculation Engine. *Diabetologia* 2017;**60**(11):2174-82.

Evans 2014

Evans JR, Michelessi M, Virgili G. Laser photocoagulation for proliferative diabetic retinopathy. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No: CD011234. [DOI: [10.1002/14651858.CD011234.pub2](https://doi.org/10.1002/14651858.CD011234.pub2)]

Fong 2003

Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Diabetic retinopathy. *Diabetes Care* 2003;**26**(Suppl 1):s99-102.

Foot 2017

Foot B, MacEwen C. Surveillance of sight loss due to delay in ophthalmic treatment or review: frequency, cause and outcome. *Eye* 2017;**31**(5):771-5.

Foroutan 2020

Foroutan F, Guyatt G, Zuka V, Vandvik PO, Alba AC, Mustafad R, et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *Journal of Clinical Epidemiology* 2020;**121**:62-70. [DOI: [10.1016/j.jclinepi.2019.12.023](https://doi.org/10.1016/j.jclinepi.2019.12.023)]

Fred Hollows Foundation 2015

Fred Hollows Foundation and the International Diabetes Federation (IDF). Diabetes eye health: a guide for health care professionals. www.worlddiabetesfoundation.org/files/diabetes-eye-health-guide-health-professionals (accessed 9 June 2020).

Fullerton 2014

Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No: CD009122. [DOI: [10.1002/14651858.CD009122.pub2](https://doi.org/10.1002/14651858.CD009122.pub2)]

Gross 2015

Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, et al. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015;**314**(20):2137-46.

Haider 2019

Haider S, Sadiq SN, Moore D, Price MJ, Nirantharakumar K. Prognostic prediction models for diabetic retinopathy progression: a systematic review. *Eye* 2019;**33**(5):702-13.

Hayden 2013

Hayden DC, van der Windt DA, Cartwright JL, Cote PC, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine* 2013;**158**(4):280-6.

Hutton 2017

Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR. Cost-effectiveness of intravitreal ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: secondary analysis from a Diabetic Retinopathy Clinical Research Network randomized clinical trial. *JAMA Ophthalmology* 2017;**135**(6):576-84.

Inoue 2019

Inoue K, Kataoka SY, Kawano S, Furukawa TA, Lois N, Watanabe N. Fenofibrate for diabetic retinopathy. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No: CD013318. [DOI: [10.1002/14651858.CD013318](https://doi.org/10.1002/14651858.CD013318)]

Keech 2007

Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;**370**(9600):1687-97.

Klein 1998

Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in Type 1 diabetes. *Ophthalmology* 1998;**105**(10):1801-15.

Klein 2008

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII:

the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology* 2008;**115**(11):1859-68.

Liu 2020

Liu Y, Li J, Ma J, Tong N. The threshold of the severity of diabetic retinopathy below which intensive glycemic control is beneficial in diabetic patients: estimation using data from large randomized clinical trials. *Journal of Diabetes Research* 2020;2020:Article ID 8765139.

Martinez-Zapata 2014

Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, Pijoán JI, Buil-Calvo JA, Cordero JA, et al. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No: CD008721. [DOI: [10.1002/14651858.CD008721.pub2](https://doi.org/10.1002/14651858.CD008721.pub2)]

Mathur 2017

Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. *BMJ Open* 2017;**7**(2):e014444.

Rücker 2008

Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I² in assessing heterogeneity may mislead. *BMC Medical Research Methodology* 2008;**8**(1):79.

Saeedi 2019

Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice* 2019;**157**:107843. [DOI: [10.1016/j.diabres.2019.107843](https://doi.org/10.1016/j.diabres.2019.107843)]

Sivaprasad 2017

Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;**389**(10085):2193-203.

Sivaprasad 2019

Sivaprasad S, Pearce E. The unmet need for better risk stratification of non-proliferative diabetic retinopathy. *Diabetic Medicine* 2019;**36**(4):424-33.

Srinivasan 2017

Srinivasan S, Raman R, Kulothungan V, Swaminathan G, Sharma T. Influence of serum lipids on the incidence and progression of diabetic retinopathy and macular oedema: Sankara Nethralaya Diabetic Retinopathy Epidemiology And Molecular genetics Study - II. *Clinical and Experimental Ophthalmology* 2017;**45**(9):894-900.

Stewart 2018

Stewart S, Lois N. Fenofibrate for diabetic retinopathy. *Asia-Pacific Journal of Ophthalmology* 2018;**7**(6):422-6.

Stitt 2016

Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A, et al. The progress in understanding and treatment of diabetic retinopathy. *Progress in Retinal and Eye Research* 2016;**51**:156-86.

Thomas 2019

Thomas RL, Halim S, Gurudas S, Sivaprasad S, Owens DR. IDF Diabetes Atlas: A review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. *Diabetes Research and Clinical Practice* 2019;**157**:107840. [DOI: [10.1016/j.diabres.2019.107840](https://doi.org/10.1016/j.diabres.2019.107840)]

Tierney 2007

Tierney JF, Stewart LA, Gherzi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**(1):16.

Turner 1998

Turner RC, Holman RR, Cull CA, Stratton I, Matthews DR, Frighi V, et al. 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* 1998;**352**(9131):837-53.

Wang 1993

Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 1993;**341**(8856):1306-9.

Wubben 2019

Wubben TJ, Johnson MW, Sohn EH, Peairs JJ, Kay CN, Kim SJ, et al. Anti-vascular endothelial growth factor therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *American Journal of Ophthalmology* 2019;**204**:13-8.

Yau 2012

Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;**35**(3):556-64.

Zhou 2018a

Zhou JB, Song ZH, Bai L, Zhu XR, Li HB, Yang JK. Could intensive blood pressure control really reduce diabetic retinopathy outcomes? Evidence from meta-analysis and trial sequential analysis from randomized controlled trials. *Diabetes Therapy* 2018;**9**(5):2015-27.

Zhou 2018b

Zhou Y, Wang C, Shi K, Yin X. Relationship between dyslipidemia and diabetic retinopathy: a systematic review and meta-analysis. *Medicine* 2018;**97**(36):e12283.

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Risk Factors] this term only
- #2 risk factor*
- #3 MeSH descriptor: [Biomarkers] this term only
- #4 biomarker*
- #5 marker*
- #6 biological marker*
- #7 MeSH descriptor: [Vascular Endothelial Growth Factor A] this term only
- #8 Vascular Endothelial Growth Factor A
- #9 VEGF
- #10 MeSH descriptor: [Intercellular Signaling Peptides and Proteins] this term only
- #11 growth factor*
- #12 MeSH descriptor: [Erythropoietin] explode all trees
- #13 erythropoietin*
- #14 EPO
- #15 retinal angiogenic factor*
- #16 MeSH descriptor: [Epidemiology] explode all trees
- #17 epidemiolog*
- #18 potential role*
- #19 (risk* or rate*) NEAR/5 (progress* or complicat*)
- #20 MeSH descriptor: [Risk Assessment] this term only
- #21 risk* NEAR/5 (assess* or stratif*)
- #22 MeSH descriptor: [Phenotype] explode all trees
- #23 phenotype*
- #24 MeSH descriptor: [Prognosis] this term only
- #25 prognos*
- #26 predict*
- #27 model*
- #28 variable*

#29 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 MeSH descriptor: [Diabetic Retinopathy] this term only
#31 proliferative diabetic retinopathy*
#32 PDR
#33 non?proliferative diabetic retinopathy*
#34 NPDR
#35 complication* adj5 (diabetic retinopathy* or DR)
#36 microvascular complication* NEAR/5 diabet*
#37 severity* NEAR/5 (diabetic retinopathy* or DR)
#38 advanced NEAR/5 (diabetic retinopathy* or DR*)
#39 severe retinopathy*
#40 MeSH descriptor: [Retinal Neovascularization] this term only
#41 new vessel*
#42 retina* NEAR/5 neo?vasculari*
#43 (neovasculari* or new vessel*) NEAR/5 (disc* or retina* or elsewhere or iris*)
#44 NVD or NVE or NVI
#45 rubeosis iridis*
#46 (vision* or sight*) NEAR/5 threat* adj5 (diabet* or retinopathy*)
#47 #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#48 MeSH descriptor: [Vitreous Hemorrhage] this term only
#49 vitreous h?emorrhage*
#50 fibro?proliferative disease*
#51 tractional retinal detachment*
#52 rhegmatogenous retinal detachment*
#53 MeSH descriptor: [Glaucoma, Neovascular] this term only
#54 neovascular glaucoma*
#55 NVG
#56 (moderate* or severe* or reduced) NEAR/5 vis*
#57 MeSH descriptor: [Blindness] this term only
#58 registered NEAR/5 blind
#59 blindness*
#60 partial* sight*
#61 #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
#62 occurrence*
#63 advancement*
#64 worsen*
#65 evolution* or evol*
#66 relationship* between
#67 MeSH descriptor: [Association] this term only
#68 MeSH descriptor: [Correlation of Data] this term only
#69 MeSH descriptor: [Incidence] this term only
#70 MeSH descriptor: [Prevalence] this term only
#71 MeSH descriptor: [Disease Progression] explode all trees
#72 natural histor*
#73 natural course*
#74 #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73
#75 29 and 47 and 61 and 74

Appendix 2. MEDLINE search strategy

1. Risk Factors/
2. risk factor*.tw.
3. Biomarkers/
4. biomarker*.tw.
5. marker*.tw.
6. biological marker*.tw.
7. Vascular Endothelial Growth Factor A/
8. Vascular Endothelial Growth Factor A.tw.
9. VEGF.tw.
10. "Intercellular Signaling Peptides and Proteins"/
11. growth factor*.tw.

12. exp Erythropoietin/
13. erythropoietin*.tw.
14. EPO.tw.
15. retinal angiogenic factor*.tw.
16. exp Epidemiology/
17. epidemiolog*.tw.
18. potential role*.tw.
19. ((risk* or rate*) adj5 (progress* or complicat*)).tw.
20. Risk Assessment/
21. (risk* adj5 (assess* or stratif*)).tw.
22. exp Phenotype/
23. phenotype*.tw.
24. Prognosis/
25. prognos*.tw.
26. predict*.tw.
27. model*.tw.
28. variable*.tw.
29. or/1-28
30. Diabetic Retinopathy/
31. proliferative diabetic retinopathy*.tw.
32. PDR.tw.
33. non?proliferative diabetic retinopathy*.tw.
34. NPDR.tw.
35. (complication* adj5 (diabetic retinopathy* or DR)).tw.
36. (microvascular complication* adj5 diabet*).tw.
37. (severity* adj5 (diabetic retinopathy* or DR)).tw.
38. (advanced adj5 (diabetic retinopathy* or DR*)).tw.
39. severe retinopathy*.tw.
40. Retinal Neovascularization/
41. (retina* adj5 neo?vasculari*).tw.
42. new vessel*.tw.
43. ((neovasculari* or new vessel*) adj5 (disc* or retina* or elsewhere or iris*)).tw.
44. (NVD or NVE or NVI).tw.
45. rubeosis iridis*.tw.
46. ((vision* or sight*) adj5 threat* adj25 (diabet* or retinopathy*)).tw.
47. or/30-46
48. Vitreous Hemorrhage/
49. vitreous h?emorrhage*.tw.
50. fibro?proliferative disease*.tw.
51. tractional retinal detachment*.tw.
52. rhegmatogenous retinal detachment*.tw.
53. Glaucoma, Neovascular/
54. neovascular glaucoma*.tw.
55. NVG.tw.
56. ((moderate* or severe* or reduced) adj5 vis*).tw.
57. Blindness/
58. (registered adj5 blind).tw.
59. blindness*.tw.
60. partial* sight*.tw.
61. or/48-60
62. occurrence*.tw.
63. advancement*.tw.
64. worsen*.tw.
65. (evolution* or evol*).tw.
66. relationship* between.tw.
67. Association/
68. "correlation of data"/
69. incidence/ or prevalence/
70. exp disease progression/
71. natural histor*.tw.
72. natural course*.tw.
73. or/62-72

74. 29 and 47 and 61 and 73

Appendix 3. Embase search strategy

1. risk factor/
2. risk factor*.tw.
3. exp marker/
4. biomarker*.tw.
5. marker*.tw.
6. vasculotropin/
7. Vascular Endothelial Growth Factor A.tw.
8. VEGF.tw.
9. growth factor/
10. growth factor*.tw.
11. erythropoietin/
12. erythropoietin*.tw.
13. EPO.tw.
14. retinal angiogenic factor*.tw.
15. exp epidemiology/
16. epidemiolog*.tw.
17. potential role*.tw.
18. ((risk* or rate*) adj5 (progress* or complicat*)).tw.
19. risk assessment/
20. exp phenotype/
21. phenotype*.tw.
22. prognosis/
23. prognos*.tw.
24. predict*.tw.
25. model*.tw.
26. variable*.tw.
27. inter?cellular signal*.tw.
28. or/1-27
29. diabetic retinopathy/ or proliferative diabetic retinopathy/
30. proliferative diabetic retinopathy*.tw.
31. PDR.tw.
32. non?proliferative diabetic retinopathy.tw.
33. NPDR.tw.
34. (complication* adj5 (diabetic retinopathy* or DR)).tw.
35. (microvascular complication* adj5 diabet*).tw.
36. (severity* adj5 (diabetic retinopathy* or DR)).tw.
37. (advanced adj5 (diabetic retinopathy* or DR)).tw.
38. severe retinopathy*.tw.
39. retina neovascularization/
40. (retina* adj5 neovasculari*).tw.
41. new vessel*.tw.
42. (neovasculari* adj5 (disc* or retina* or elsewhere or iris*)).tw.
43. (NVD or NVE or NVI).tw.
44. iris rubeosis/
45. rubeosis iridis*.tw.
46. ((vision* or sight*) adj5 threat* adj5 (diabet* or retinopathy*)).tw.
47. or/29-46
48. vitreous hemorrhage/
49. vitreous h?emorrhage*.tw.
50. fibro?proliferative disease*.tw.
51. tractional retinal detachment*.tw.
52. rhegmatogenous retinal detachment*.tw.
53. neovascular glaucoma/
54. neovascular glaucoma*.tw.
55. NVG.tw.
56. ((moderate* or severe* or reduced) adj5 vis*).tw.
57. blindness/
58. (registered adj5 blind).tw.

59. blindness.tw.
60. partial* sight*.tw.
61. or/48-60
62. occurrence*.tw.
63. advancement*.tw.
64. worsen*.tw.
65. (evolution* or evol*).tw.
66. relationship* between.tw.
67. association/
68. data correlation/
69. incidence/
70. prevalence/
71. disease exacerbation/
72. natural histor*.tw.
73. disease course/
74. natural course*.tw.
75. or/62-74
76. 28 and 47 and 61 and 75

Appendix 4. CHARMS-PF Data extraction

Study	
Study design	Source of data (e.g. cohort, case-control, randomised trial, or registry data)
	Dates
Participants	Participant eligibility and recruitment method (e.g. consecutive participants, location, number of centres, setting, inclusion and exclusion criteria)
	Participant description
	Details of treatment received, if relevant
Outcomes to be predicted	Definition of outcome
	Method of measurement
	Time of outcome occurrence
Prognostic factors (index and comparator)	Type of prognostic factors
	Definition and method of measurement for prognostic factors
	Timing of prognostic factor measurement
	Handling of prognostic factors in the analysis
Sample size	Was a sample size calculation conducted, and if so, how?
	Number of participants
	Number of outcomes
	Number of outcomes in relation to number of candidate prognostic factors (outcomes per variable)
Missing data	Number of participants with missing data for each prognostic factor of interest

(Continued)

	Details of attrition and, for time-to-event outcomes, number of censored observations
	Handling of missing data
Analysis	Modelling method of analysis
	How modelling assumptions were checked: in particular, for time-to-event outcomes and the analysis of hazard ratios, the method for assessing non-proportional hazards (non-constant hazard ratios over time)
	Method for selection of prognostic factors for inclusion in multivariable modelling (e.g. all candidate prognostic factors considered, preselection of established prognostic factors, retain only those significant from univariable analysis)
	Method for selection or exclusion of prognostic factors (including those of interest and those used as adjustment factors) during multivariable modelling (e.g. backward or forward selection, or full model approach including all factors regardless) and criteria used for any selection or exclusion (e.g. P value, Akaike information criterion)
Results	Unadjusted and adjusted prognostic effect estimates (e.g. risk ratios, odds ratios, hazard ratios, mean differences) for each prognostic factor of interest, and the corresponding 95% confidence interval (or variance or standard error)
	For each extracted adjusted prognostic effect estimate of interest, the set of adjustment factors used

Appendix 5. QUIPS

Domains	Signalling items	'Risk of bias' ratings
1. Study participation	(a) Adequate participation in study by eligible individuals	Relationship between PF and outcome -
	(b) Description of target population	High: very likely to be different for participants and eligible non-participants
	(c) Description of baseline study sample	Moderate: may be different for participants and eligible non-participants
	(d) Adequate description of recruitment process	Low: unlikely to be different for participants and eligible non-participants
	(e) Adequate description of period and place of recruitment	
	(f) Adequate description of inclusion/exclusion criteria	
2. Study attrition	(a) Adequate response rate for study participants	Relationship between PF and outcome -
	(b) Description of process for collecting information on participants who dropped out	High: very likely to be different for completing and non-completing participants

(Continued)

	(c) Reasons for loss to follow-up provided	Moderate: may be different for completing and non-completing participants
	(d) Adequate description of participants lost to follow-up	Low: unlikely be different for completing and non-completing participants
	(e) No important differences between participants who completed the study and those who dropped out	
3. Prognostic factor (PF) measurement	(a) Clear definition of PF provided	Measurement of PF -
	(b) Method of PF measurement is adequately valid and reliable	High: very likely to be different for different levels of outcome of interest
	(c) Continuous variables are reported	Moderate: may be different for different levels of outcome of interest
	(d) Method and setting of measurement of PF is identical for all participants	Low: unlikely to be different for different levels of outcome of interest
	(e) Adequate proportion of study sample has complete data for PF	
	(f) Appropriate methods of imputation used for missing PF data	
4. Outcome measurement	(a) Clear definition of outcome provided	High: outcome measurement very likely to be different related to baseline level of PF
	(b) Method of outcome measurement is adequately valid and reliable	Moderate: outcome measurement may be different related to baseline level of PF
	(c) Method and setting of outcome measurement is identical for all participants	Low: outcome measurement unlikely to be different related to baseline level of PF
5. Adjustment for other prognostic factors	(a) All other important PFs measured	Observed effect of PF on outcome -
	(b) Clear definitions of important PFs measured provided	High: very likely to be distorted by another factor related to PF and outcome
	(c) Measurement of all important PFs adequately valid and reliable	Moderate: may be distorted by another factor related to PF and outcome
	(d) Measurement and setting of PF measurement identical for all participants	Low: unlikely to be distorted by another factor related to PF and outcome
	(e) Appropriate methods are used to deal with missing values of PFs	
	(f) Important PFs accounted for in study design	
	(g) Important PFs accounted for in analysis	
6. Statistical analysis and reporting	(a) Sufficient presentation of data to assess adequacy of analytic strategy	Reported results -

(Continued)

(b) Strategy for model building appropriate and based on a conceptual framework or model	High: very likely to be spurious or biased related to analysis or reporting
(c) Selected statistical model adequate for design of study	Moderate: may be spurious or biased related to analysis or reporting
(d) No selective reporting of results	Low: unlikely to be spurious or biased related to analysis or reporting

HISTORY

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CONTRIBUTIONS OF AUTHORS

JP and NL drafted the Background, Objectives, Criteria for considering studies for this review, Search methods, and Data collection (Selection of studies, Data extraction management, Assessment of risk of bias) components of the Methods section of the protocol.

RA and YT drafted the Measures of association or predictive performance measures to be extracted, Dealing with missing data, Assessment of heterogeneity, Assessment of reporting deficiencies, Data synthesis and meta-analysis approaches, Sensitivity analysis, and Conclusions and 'Summary of findings' components of the Methods section of the protocol.

RH, JL, and JE reviewed the draft protocol and provided comments and input to it.

JP produced the final manuscript, which was reviewed and approved by all authors prior to submission.

NL conceived the idea for the review.

All authors provided input to the plan and methodological aspects of the review.

DECLARATIONS OF INTEREST

JP: None known.

RA: None known.

RF: None known.

RH has participated in Novartis Advisory boards relating to biomarkers and clinical trial outcomes for age-related macular degeneration.

JL: None known.

JE: None known.

YT: None known.

NL: None known.

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