

## Diabetic Retinopathy: management and monitoring

**[D] Evidence reviews for the effectiveness of lipid modification therapies and antihypertensive medicines**

*NICE guideline <number>*

*Evidence reviews underpinning recommendations 1.1.6 to 1.1.10 and research recommendations in the NICE guideline*

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*These evidence reviews were developed  
by Guideline Development Team*



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# Effectiveness of lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy

## 1.1 Review question

What is the effectiveness of lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy?

### 1.1.1 Introduction

Lipid modification therapies and antihypertensive medicines are both important for the treatment or prevention of comorbidities related to diabetes. Antihypertensive medicines are used to lower blood pressure and are important because hypertension is a common comorbidity for people with diabetes. Hypertension is also known to be a risk factor for the development and progression of diabetic retinopathy. Lipid modification therapies can be used to reduce the risk of developing cardiovascular disease. It is important to understand whether these treatments are also effective at reducing the risk of progression of non-proliferative diabetic retinopathy, as this can help to avoid or reduce more serious consequences, such as vision loss, that are associated with progression.

Given the common use of these treatments for people with diabetes, this review aims to assess whether they are also effective and safe methods of reducing the risk of progression of non-proliferative diabetic retinopathy.

### 1.1.2 Summary of the protocol

The protocols for the evidence reviews are summarised in [Table 1](#). Please see full protocols in [Appendix A](#)

**Table 1: PICO table for lipid modification therapies and antihypertensive medicines**

<b>Population</b>	People with non-proliferative diabetic retinopathy
<b>Interventions</b>	<p>Blood pressure control interventions (as described in <a href="#">Do et al. (2023)</a>):</p> <ul style="list-style-type: none"> <li>• Strict blood pressure control, alone or in combination with other interventions, when compared with less strict blood pressure control</li> <li>• Any blood pressure control, when compared with placebo</li> <li>• Any class of anti-hypertensive medicine compared with another class of anti-hypertensive medicine</li> </ul> <p>Fibrates (limited to those with a UK marketing authorisation):</p> <ul style="list-style-type: none"> <li>• Bezafibrate, ciprofibrate, gemfibrozil</li> <li>• Fenofibrate (as described in Cochrane review): (any dose/regimen)</li> </ul> <p>Statins:</p> <ul style="list-style-type: none"> <li>• Statin medications (for example atorvastatin, simvastatin)</li> </ul>

<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Statins in combination with another lipid modification therapy or antihypertensive medication.</li> </ul> <p>Blood pressure control interventions (as described in <a href="#">Do et al. (2023)</a>)</p> <ul style="list-style-type: none"> <li>• Less strict blood pressure control when compared with strict blood pressure control.</li> <li>• Placebo</li> <li>• Another class of anti-hypertensive medicine when compared with a class of anti-hypertensive medicine.</li> </ul> <p>Fibrates</p> <ul style="list-style-type: none"> <li>• Placebo or observation (no treatment)</li> </ul> <p>Statins:</p> <ul style="list-style-type: none"> <li>• Fibrate (any dose/regimen)</li> <li>• Any blood pressure control intervention</li> <li>• Placebo or observation (no treatment)</li> </ul>
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Visual acuity             <ul style="list-style-type: none"> <li>○ For blood pressure control interventions reported as proportion with reduction of visual acuity by three or more lines in both eyes on a logMAR chart.</li> <li>○ For fenofibrate reported as mean visual acuity and proportion of participants with a reduction in visual acuity of 10 ETDRS letters or more (equivalent to 2 or more lines on a logMAR chart)</li> <li>○ For statins and other fibrates (original review), reported as mean visual acuity or proportion participants with a reduction in visual acuity of 2 or 3 lines on a logMAR chart, as reported by the studies.</li> </ul> </li> <li>• Incidence of proliferative diabetic retinopathy</li> <li>• Incidence of diabetic macular oedema</li> <li>• Incidence of diabetic macular ischaemia</li> <li>• Vision related quality of life (measured using validated tool)</li> </ul>

25

### 26 1.1.3 Methods and process

27 This evidence review was developed using the methods and process described in  
 28 [Developing NICE guidelines: the manual](#) and the [methods document](#) for the diabetic  
 29 retinopathy guideline.

30 Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).  
 31 Methods specific to this review question are described in the review protocol in [Appendix A](#).

32 This evidence review used data collected as part of 2 Cochrane reviews: [Do et al. \(2023\)](#)  
 33 which assessed blood pressure interventions and [Kataoka et al. \(2023\)](#) which assessed the  
 34 use of fenofibrates. Both studies were assessed as high quality and partially applicable to the  
 35 review (see [Appendix D](#)). Information for these parts of the review were therefore used  
 36 directly from the Cochrane reviews (see [Table 2 in the methods document](#)), rather than  
 37 undertaking a new literature search. The reviews were considered partially applicable  
 38 because they included a wider population than the population for this review (people with  
 39 mild non-proliferative retinopathy or proliferative diabetic retinopathy at baseline). Because

40 they included a wider population than in this review, an additional NICE search was not  
41 required.

42 Studies from the Cochrane reviews were assessed to determine whether they matched the  
43 inclusion criteria in this review protocol. Both studies from the Cochrane review on fibrates,  
44 [Kataoka et al. \(2023\)](#), met the inclusion criteria for this review. Twenty-nine RCTs were  
45 included in the Cochrane review for blood pressure control ([Do et al. 2023](#)) but of those only  
46 6 met the inclusion criteria for this review. See [Appendix J](#) for the reasons that the other  
47 studies in Do et al. (2023) were excluded from this review.

48 The Cochrane review on the effectiveness of fibrates ([Kataoka et al., 2023](#)) reported that  
49 studies aimed at treating existing diabetic macular oedema were excluded. This was not  
50 specified in the original Cochrane review protocol and was not a criterion for this current  
51 review. The NICE guideline team therefore re-examined these studies to see if they matched  
52 the criteria in the review protocol for the current review. None of these matched the  
53 population for this review and so no additional studies were included. Reasons for exclusion  
54 of the remaining 18 studies are documented in the excluded studies list ([Appendix J](#)).

55 All data from the fenofibrates, Cochrane review ([Kataoka et al. 2023](#)) was used in this  
56 review, and so results, quality assessments and applicability assessments were taken  
57 directly from the Cochrane review. Only some of the studies from the Cochrane review on  
58 blood pressure control ([Do et al. 2023](#)) matched the NICE review protocol and so the  
59 Cochrane review was used as a source of data. Data from each relevant study was extracted  
60 and re-analysed using NICE methods to produce forest plots and GRADE tables. Risk of  
61 bias and applicability assessments for individual studies were taken from the Cochrane  
62 review.

#### 63 **1.1.4 Effectiveness evidence**

##### 64 **1.1.4.1 Included studies.**

65 A systematic search was conducted to identify studies that were not covered by the [Do et al.](#)  
66 [2023](#) and [Kataoka et al 2023](#). Cochrane reviews. This search looked for studies evaluating  
67 the effectiveness of statins and studies evaluating fibrates other than fenofibrate.

68 For statins, the systematic search identified 326 records. These were screened on title and  
69 abstract, with 53 full-text papers ordered as potentially relevant studies. After full-text  
70 screening, five studies matched the inclusion criteria and were included in the review. For  
71 fibrates the systematic search identified 106 records. These were screened on title and  
72 abstract, with no full-text papers ordered as relevant studies. For blood pressure control  
73 interventions, six studies that were identified by the Cochrane review ([Do et al. 2023](#))  
74 matched the inclusion criteria in this review protocol. In total, 13 studies matched the  
75 inclusion criteria for this review:

- 76 • For blood pressure control interventions, 6 studies that from were identified by the  
77 Cochrane review ([Do et al. 2023](#)) matched the inclusion criteria in this review  
78 protocol. All 6 compared blood pressure control to placebo.
- 79 • For statins, 5 studies from the NICE search matched the inclusion criteria and were  
80 included in this review. Three studies compared statins to placebo, 1 study compared  
81 statins plus fibrate to statins, and 1 study compared intensive statin therapy to  
82 standard statin therapy.
- 83 • For fenofibrates, 2 studies were identified by the [Kataoka et al. 2023](#) Cochrane  
84 review and both matched the inclusion criteria in this review protocol. Both studies



85 compared fenofibrates to placebo and reported outcomes for a subgroup of people  
86 with diabetic retinopathy at baseline.

87 For the study selection process for statins, please see the PRISMA flow diagram in [Appendix](#)  
88 [C](#). For the study selection process for blood pressure control interventions, see Figure 1 in  
89 the Cochrane review ([Do et al. 2023](#)). For the study selection process for fibrates, see Figure  
90 1 in the Cochrane review ([Kataoka et al. 2023](#)).

91 For the full evidence tables and full GRADE profiles for included studies, please see  
92 [Appendix D](#) and [Appendix F](#).

#### 93 **1.1.4.2 Excluded studies**

94 See [Appendix J](#) for a list of excluded studies with reasons for exclusion.

95 **1.1.5 Summary of studies included in the Effectiveness evidence.**96 **Table 2: Blood pressure control intervention studies**

97 See the Cochrane review ([Do et al. 2023](#)) for the full evidence tables for each of the studies for blood pressure control interventions. The  
 98 information was extracted by Cochrane from the original studies.

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
ADVANCE/AdRem  14 countries in Asia, Australia, Europe, and North America (39 centres)	RCT 4.1 year follow up	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• all participants in ADVANCE (55 years or older at recruitment; diagnosed with type 2 diabetes at age 30 years or older; history of at least one of the following conditions: major cardiovascular disease, risk factors including history of major</li> <li>• microvascular disease, current cigarette smoking, elevated total cholesterol (&gt; 6.0 mmol/L), low HDL cholesterol (&lt; 1.0 mmol/L), microalbuminuria</li> <li>• diagnosed with type 2 diabetes 10 years or more preceding entry into the study or age 65 years or older at recruitment.</li> <li>• an indication for an ACE inhibitor who enrolled at centres with retinal cameras were eligible to participate.</li> </ul> <p><b>Exclusion criteria for ADVANCE:</b></p>	<ul style="list-style-type: none"> <li>• N= 623</li> <li>• ACE inhibitor plus diuretic: Perindopril (2 mg) plus indapamide (0.625 mg) daily at randomization</li> <li>• doubled to perindopril (4 mg) plus indapamide (1.25 mg) after 3 months</li> </ul>	<ul style="list-style-type: none"> <li>• Placebo N=618</li> </ul>	<p>Primary outcome, as specified for this review:</p> <ul style="list-style-type: none"> <li>• progression of diabetic retinopathy <math>\geq</math> 2 steps by ETDRS classification</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<ul style="list-style-type: none"> <li>definite indication or contraindication for the active study treatments or a definite indication for a HbA1c target of <math>\leq 6.5\%</math>, long-term insulin therapy at study entry or participating in a different clinical trial.</li> </ul> <p><b>in addition, for ADVANCE/Amdram:</b></p> <ul style="list-style-type: none"> <li>previous ophthalmological intervention or inability to obtain good quality photographs due to either severe cataract or inadequate pupil dilation (<math>&lt; 4</math> mm)</li> </ul>			
<p>DIRECT Protect 1</p> <p>30 countries; Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, New Zealand, Poland, Portugal, Romania, Russian Federation, South Africa, Spain,</p>	<p>RCT</p> <p>4.8 years follow up</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>age 18 to 55 years, no restriction on gender, younger than 36 years of age when type 1 diabetes diagnosed, duration of 1 to 20 years, continuously used insulin</li> <li>within a year of diagnosis, no microalbuminuria, SBP <math>\leq 130</math> mm Hg and DBP <math>\leq 85</math> mm Hg</li> <li>and a diabetic retinopathy grading <math>\geq 20/10</math> (mild, non-proliferative), up to <math>\leq 47/47</math></li> <li>(Moderately severe non-proliferative) on the ETDRS scale based on 7-field stereo retinal photographs.</li> </ul>	<ul style="list-style-type: none"> <li>(N = 951) Angiotensin receptor antagonist only Candesartan cilexetil 16 mg (ARB)</li> <li>Daily dose doubled or halved after one month; then doubled or halved based on tolerability</li> </ul>	<ul style="list-style-type: none"> <li>(N = 954) placebo</li> </ul>	<p><b>Primary outcome,</b></p> <p>as specified for this review:</p> <ul style="list-style-type: none"> <li>progression of retinopathy</li> </ul> <p>Secondary outcomes, as specified for this review:</p> <ul style="list-style-type: none"> <li>progression to CSME and/or PDR per the ETDRS protocol</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Sweden, Turkey, United Kingdom		<p><b>Exclusion criteria:</b> eye conditions precluding capture of gradable retinal photographs (Open-angle glaucoma, cataracts obscuring view of retina), patients with valvular stenosis, history of heart attack or stroke, pregnant or lactating women, patients with renal impairment defined as serum creatinine <math>\geq 110</math> <math>\mu\text{mol/L}</math> for women and <math>\geq 130</math> <math>\mu\text{mol/L}</math> for men</p>			
DIRECT Protect 2  Austria, Belgium, Croatia, Finland, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Romania, United Kingdom	RCT  2 years follow up.	<p><b>Inclusion criteria:</b> men and women (on contraception or postmenopausal) aged 20 to 59 years: IDDM defined as diagnosis before 36 years of age and continuous insulin required within 1 year of diagnosis, resting DBP 75 to 90 mm Hg, SBP <math>\leq 155</math> mm Hg</p> <p><b>Exclusion criteria:</b> renal artery stenosis, cardiac valve obstruction, accelerated hypertension, recent myocardial infarction, CABG, stroke, CHF, abnormal renal function (creatinine <math>&gt; 1.8</math> mg/dL), postural hypotension, or idiosyncratic reactions to ACE inhibitors</p>	<ul style="list-style-type: none"> <li>(N=265) ACE inhibitor only 10 mg/day lisinopril,</li> </ul>	<ul style="list-style-type: none"> <li>(N=265) Placebo</li> </ul>	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>retinopathy progression by at least 2 levels; retinal photographs at baseline and 24 months. classification was on a 5-level scale, using the EURODIAB diabetic retinopathy classification. from photos</li> </ul> <p><b>Secondary outcome:</b></p> <ul style="list-style-type: none"> <li>progression to PDR</li> </ul>
Chew, 2014  (ACCORD)	RCT  4 years follow up	<p><b>Inclusion criteria:</b></p>	(N = 314) The intensive treatment	(N=330) The standard	<b>Primary outcome</b>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
USA and Canada		<p>People with an HDL cholesterol level of less than 55 mg per decilitre; (1.4 mmol per litre) for women and for black ethnicity. Less than 50 mg per decilitre (1.3 mmol per litre) for all other people.</p> <p><b>Exclusion criteria:</b> People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded.</p> <p>NOTE: only outcomes for which a subgroup analysis of people with retinopathy at baseline were included, as the whole trial population did not match the inclusion criteria for this review.</p>	<p>arm targeted systolic blood pressure &lt;120 mmHg,</p> <p>N= for subgroup with diabetic retinopathy at baseline Microaneurysm or mild DR 1 eye, no DR or Ma only in other N= 173</p> <p>Mild/moderate NPDR N=99</p> <p>Moderate/moderately severe NPDR N=42</p>	<p>treatment arm targeted systolic blood pressure &lt;140 mmHg.</p> <p>N= for subgroup with diabetic retinopathy at baseline)</p> <p>Microaneurysms or mild DR 1 eye, no DR or Ma only in other N=197</p> <p>Mild/moderate NPDR N=95</p> <p>moderate/moderately severe NPDR N=29</p>	<ul style="list-style-type: none"> <li>Progression of DR (ETDRS)</li> </ul>
JEDIT  Japan (39 centres)	RCT  6 years follow up	<p><b>Inclusion criteria:</b> Age 65 - 85 years; HbA1c ≥ 7.9% OR 7.4% to &lt; 7.9% AND BP &gt; 130/85mmHg; other criteria related to cholesterol, etc.</p> <p><b>Exclusion criteria:</b> VA &lt; 20/200 and history of glaucoma; if grading of the ocular fundus was not possible, eye was excluded from analysis of DR (“940</p>	<ul style="list-style-type: none"> <li>(N = 588) Intensive BP monitoring; goals: HbA1c &lt; 6.9%; BMI &lt; 25 kg/m<sup>2</sup>; BP &lt;130/85 mm Hg; HDL-C &gt; 40 mg/dL; serum triglycerides &lt; 150 mg/dL, serum total cholesterol &lt; 120 mg/dL for participants without CHD.</li> </ul>	<p>(N = 585) Conventional BP monitoring: usual baseline treatment for diabetes, hypertension, and dyslipidaemia without special treatment goals, i.e., no intervention</p>	<p><b>Primary outcome:</b> progression of DR</p>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		eyes of 940 participants met the inclusion criteria"); if MI or stroke in < 6 months, excluded	<ul style="list-style-type: none"> <li>For participants with CHD: LDL-C &lt; 100 mg/dL</li> <li>Physicians prescribed oral hypoglycaemic drugs or insulin and atorvastatin to achieve targets.</li> </ul>		
UKPDS/HDS United Kingdom	RCT 9.3 Year follow up	<p><b>Inclusion criteria:</b> Type 2 diabetes and participating in the UKPDS, mean of blood pressure readings from 3 consecutive visits &gt; 160 mm Hg SBP and/or a DBP &gt; 90 mm Hg when not receiving treatment for hypertension or SBP &gt; 150 mm Hg and/or a DBP &gt; 85 mm Hg on treatment for hypertension; participants with SBP ≥ 200 mmHg and/or DBP ≥ 105 mmHg on any single occasion was eligible for randomisation.</p> <p><b>Exclusion criteria:</b> Requirement for strict blood pressure control due to a previous stroke, accelerated hypertension, ketonuria &gt; 3 mmol/L; cardiac or renal failure; those who required beta-blockade (myocardial infarction in the previous year or current angina); severe vascular disease with more than one major vascular episode;</p>	<ul style="list-style-type: none"> <li>LTBP control policy aiming for blood pressure &lt; 150/85 mm Hg; random allocation to either ACE inhibitor or a beta-blocker.</li> <li>captopril (ACE inhibitor) starting at 25 mg twice daily, increasing to 50 mg twice daily.</li> <li>Atenolol (beta-blocker) starting at 50 mg daily, increasing to 100 mg daily.</li> <li>In both groups, if blood pressure targets were not met, other agents were added; recommended sequence: furosemide 20 mg (maximum 40 mg) twice a day, slow release nifedipine 10 mg</li> </ul>	LTBP control policy aiming for blood pressure ≤ 180/105 mm Hg but avoiding therapy with ACE inhibitors or beta-blockers.	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>Progression of retinopathy defined as a 2-step or greater change by ETDRS grading.</li> </ul> <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> <li>visual loss defined as the best vision in either eye, deteriorating by 3 lines or more on the ETDRS chart (clinical records);</li> <li>progression to PDR or photocoagulation</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		contraindication to beta-blockade (with conditions such as asthma, intermittent claudication, foot ulcers or amputations); and severe concurrent illness.	(maximum 40 mg) twice a day, methyldopa 250 mg (maximum 500 mg) twice a day, and prazosin 1 mg (maximum 5 mg) three times a day		

99 **Table 3: Statins included studies**

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Gupta, 2004 India	RCT 18 week follow up	<b>Inclusion criteria:</b> People with noninsulin dependent diabetes mellitus with non-proliferative diabetic retinopathy and macular oedema characterized by the presence of retinal thickening within one disc diameter of the centre of macula that was associated with hard exudates of grade 4 or more in field (1) diabetes mellitus of at least 5 years' duration. (2) abnormal baseline lipid profile (serum cholesterol 200 mg/dl, low-density lipoprotein [LDL] 100 mg/dl, or serum triglycerides 200 mg/dl); or (3) non proliferative diabetic retinopathy with clinically significant macular oedema having hard exudates of at least grade 4 in field	Atorvastatin (N = 15) 10 mg/day Both groups also received Nd Yag Green laser (532 Nm)	Placebo (N = 15) (n=15) Both groups also received Nd Yag Green laser (532 Nm)	<b>Primary outcome</b>  <ul style="list-style-type: none"> <li>• Visual acuity</li> <li>• Progression of DR (macular oedema, distribution of hard exudates)</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p><b>Exclusion criteria:</b>                      People with macular ischemia, pseudophakia, poorly controlled hypertension, associated vascular occlusions, media opacities, debilitating systemic diseases, coronary artery diseases, and any hepatic or muscular diseases were excluded from the study, as were pregnant patients</p>			
Murakami, 2021 Japan	RCT – A prespecified ophthalmology subgroup 3 years follow up	<p><b>Inclusion criteria:</b>                      Patients in the EMPATHY study (Age at least 30 years, Man; or woman who not of child-bearing potential during the study, Outpatient, Hypercholesterolemia with LDL-C<math>\geq</math>120 mg/dL for previously untreated patients or <math>\geq</math>100 mg/dL for those treated with a single statin or other lipid-lowering drug, Type 2 diabetes, No history of CAD (myocardial infarction, angina, or coronary revascularization) who had seven-field fundus photographs taken at enrolment and after three years (36 <math>\pm</math> 3 months) were eligible for participation in sub study</p> <p><b>Exclusion criteria:</b></p>	<p><i>Intervention: (N =85)                      Patients were randomly assigned to oral intensive statin therapy (targeting LDL-C below 70 mg/dL)</i></p>	<p><i>Comparator: (N =72)                      standard statin therapy (targeting LDL-C between 100 and 120 mg/dL), placebo</i></p>	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>Incidence of DR (ETDRS)</li> <li>Visual acuity (Logarithm of the Minimum Angle of Resolution, LogMAR)</li> </ul>



Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p>People with a history of hypersensitivity to statins, History of drug-associated muscle disorder, History of CAD (myocardial infarction, angina, or coronary revascularization), History of stroke (including revascularization), Symptomatic PAD, Uncontrolled hypertension with DBP <math>\geq</math> 120 mmHg or SBP <math>\geq</math> 200 mmHg, or hypertensive emergency vii) New York Heart Association class M or higher, Valvular heart disease with serious hemodynamic abnormality, Hypercholesterolemia treated with two or more lipid-lowering drugs, Familial hypercholesterolemia, Serious coexisting illness such as malignant tumour, or severely limited life expectancy (patients are eligible if they received no treatment for at least 5 years and have experiences no relapse of malignancy), Renal failure necessitating transplantation or dialysis, Patient is pregnant, could be pregnant, or wishes to become pregnant during the study</p>			
<p>Narang, 2012  India</p>	<p>RCT 6 months follow up</p>	<p><b>Inclusion criteria:</b>  People with non-proliferative diabetic retinopathy (NPDR) with CSM, Diabetic patients with normal lipid</p>	<p><i>Intervention: (N =15) Group A patients were administered Atorvastatin (daily dose of 20 mg) throughout the study period</i></p>	<p><i>Comparator: (N =15) Group B patients were given placebo during study period</i></p>	<p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Visual acuity</li> <li>• Progression of DR (distribution of hard exudates)</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p>profile i.e., total cholesterol &lt; 190mg %, LDL &lt; 115mg %, HDL &gt; 40mg % and serum triglycerides &lt; 180mg In case of bilateral CSME, worse eye was included in the study.</p> <p><b>Exclusion criteria:</b></p> <p>People with significant media opacities that precluded fundus photography / fundus fluorescein angiography, any other ocular ailment or ocular or systemic surgery within three months before randomization, diabetic retinopathy with macular ischemia, cystoid macular oedema, proliferative diabetic retinopathy, neovascularization of iris, very severe non proliferative diabetic retinopathy, cases of myopathy, hepatic disease, myocardial infarction or other heart ailments, uncontrolled hypertension, nephropathy (serum creatinine &gt; 2 mg %), anaemia with haemoglobin less than 10gm %, debilitating systemic illness and uncontrolled blood sugar level., pregnant females, premenopausal females, patients with acute liver or renal disease, idiopathic lung fibrosis or patients who were already on statins or immunosuppressants.</p>	<p><i>starting four weeks prior to laser treatment.</i></p>		

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Sen, 2007	RCT 3 month follow up	<p><b>Inclusion criteria:</b> People with non-proliferative diabetic retinopathy with no clinically significant macular oedema Patients with diabetes mellitus (Type 1 and 2) with DR attending the ophthalmology and medicine out-patients departments were eligible for the study. Ophthalmologic inclusion criteria were:</p> <ol style="list-style-type: none"> <li>1. non-clinically significant macular oedema either in one or in both eyes (hard exudates and retinal thickening at least 500 away from fovea. Hard exudates and macular oedema had to be either 'definite' or 'questionable' as per ET DRS grading).</li> <li>2. VA 6/24 or better in one or both eyes.</li> <li>3. Leaking capillaries, intra-retinal microvascular abnormalities (IRMAs), and/or microaneurysms at least 500 away from fovea in one or both eyes.</li> <li>4. No laser photocoagulation in last year.</li> <li>5. Absence of clinically significant macular oedema (CSME), proliferative DR, age-related macular degeneration, any other macular pathology (excluding</li> </ol>	<i>Intervention: (N =25) simvastatin 20-mg per day</i>	<i>Comparator: (N =25) placebo</i>	<p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• <i>Incidence of DR (macular oedema)</i></li> <li>• <i>Visual acuity</i></li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		diabetic macular oedema), any media opacity (cataract, corneal opacity, and vitreous haemorrhage), or glaucoma.  <b>Exclusion criteria:</b> People showing either mild background DR or proliferative DR or CSME was excluded			

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106 **Table 4: Fibrates included studies**

107 See the Cochrane review ([Kataoka et al. 2023](#)) for the full evidence tables for each of the studies for the use of fibrates.

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
FIELD Ophthalmology sub study  Australia, Finland, and New Zealand	RCT  5 years follow up	<b>Inclusion criteria:</b> 1. Male or female, aged 50–75 years 2. T2D with age at diagnosis >35 years (currently using any of diet, tablets, or insulin); for Maori, Pacific Islanders, Australian Aborigines and Torres Strait	<i>Oral fenofibrate, 200mg/day (n=512)</i>  <i>Retinopathy at baseline</i> <i>Overt retinopathy, 105 (20.5%)</i> <i>DR status none, 407 (79.5%)</i>	<i>Placebo (n=500)</i>  <i>Retinopathy at baseline</i> <i>Overt retinopathy, 103 (20.6%)</i> <i>DR status none, 397 (79.4%)</i>	<i>Reported for subpopulation with diabetic retinopathy at baseline:</i> <ul style="list-style-type: none"> <li><i>Progression of DR</i></li> <li><i>Only reported for whole population so not included in this review:</i></li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p>Islanders, the eligible age of diagnosis was &gt;25 years, provided there had been at least 1 year of treatment without insulin.</p> <p>3. On the basis of diabetes, considered to be at higher risk for coronary heart disease than the general population</p> <p>4. No clear indication for any cholesterol-lowering treatment: the patient was not already taking any cholesterol-lowering drug and neither the patient nor the patient's doctor considered there to be any definite need to do so.</p> <p>5. T-chol level 3 to 6.5 mmol/L, plus either</p> <p>6. A T-chol-to-HDL cholesterol ratio of <math>\geq 4.0</math></p> <p>7. A blood triglyceride level &gt;1.0 mmol/L</p> <p>8. No clear contraindication to study therapy in the view of the treating physician</p> <p>9. No other predominant medical problem that might limit compliance with 5 years of study treatment or compromise long-term participation and clinic attendance in the trial.</p> <p>10. Two-field colour fundus photographs of both eyes showed no evidence of PDR, severe NPDR,</p>	<p><i>DR status mild, 88 (17.2%)</i></p> <p><i>DR status moderate NPDR, 14 (2.7%)</i></p> <p><i>DR status severe NPDR, 3 (0.6%),</i></p>	<p><i>DR status mild, 78 (15.6%)</i></p> <p><i>DR status moderate NPDR, 21 (4.2%)</i></p> <p><i>DR status severe NPDR, 4 (0.8%)</i></p>	<ul style="list-style-type: none"> <li>• <i>Incidence of overt retinopathy</i></li> <li>• <i>Incidence of DMO</i></li> <li>• <i>Laser treatment</i></li> <li>• <i>Vitrectomy</i></li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p>clinically significant DMO, or indication for, or evidence of a history of laser treatment at a screening examination done during the placebo run-in phase.</p> <p><b>Exclusion criteria:</b>                      Individuals were not eligible if they had any of the following characteristics:</p> <ol style="list-style-type: none"> <li>1. Serum triglyceride &gt;5 mmol/L in the baseline visit fasting blood sample</li> <li>2. Concurrent treatment with any other lipid-lowering agent</li> <li>3. Serum creatinine &gt;130 µmol/L</li> <li>4. Known chronic liver disease, transaminases &gt;2 × upper limit of normal or symptomatic gallbladder disease</li> <li>5. MI or hospital admission for unstable angina within 3 months</li> <li>6. Female, of child-bearing potential, unless sterilized or on reliable approved methods of contraception, including oral contraceptives.</li> <li>7. Concurrent cyclosporin treatment (or a condition likely to result in organ transplantation and the need for cyclosporin during the next 5 years)</li> </ol>			

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		<p>8. Known allergy to any fibrate drug or known photosensitivity</p> <p>9. Unwilling or unable to consent to enter the study, with the understanding that follow-up was planned to continue for more than 5 years.</p> <p>10. A number of other ocular pathologies or technical problems</p> <p>NOTE: Data was only included in this review for outcomes that were reported for people with diabetic retinopathy at baseline</p>			
<p>Chew, 2014  (ACCORD)  USA and Canada</p>	<p>RCT 4 years follow up</p>	<p><b>Inclusion criteria:</b></p> <p>People with an HDL cholesterol level of less than 55 mg per decilitre; (1.4 mmol per liter) for women and for black ethnicity. Less than 50 mg per deciliter (1.3 mmol per liter) for all other people.</p> <p><b>Exclusion criteria:</b></p> <p>People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded.</p> <p>NOTE: only outcomes for which a subgroup analysis of people with retinopathy at baseline were</p>	<p>(N = 806, N=399 for subgroup with diabetic retinopathy at baseline) Fenofibrate 160 mg/day plus simvastatin</p> <p>Ma or mild DR 1 eye, no DR or Ma only in other N=264</p> <p>mild/moderate NPDR N=88</p> <p>moderate/moderately severe NPDR N=47</p>	<p>(N=787, N=402 for subgroup with diabetic retinopathy at baseline) Placebo plus simvastatin</p> <p>Ma or mild DR 1 eye, no DR or Ma only in other N=258</p> <p>mild/moderate NPDR N=104</p> <p>moderate/moderately severe NPDR N=40</p>	<p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Progression of DR (ETDRS)</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		included, as the whole trial population did not match the inclusion criteria for this review.			

108 See [Appendix D](#) for full evidence tables.

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110 **1.1.6 Summary of the Effectiveness evidence**

111 Effects have been labelled as favouring one or other intervention when the confidence intervals do not cross the line of no effect. Effects are  
112 labelled 'could not differentiate' when the confidence intervals cross the line of no effect.

113 **Blood pressure control interventions**114  
115 **More blood pressure control vs less blood pressure control**116 **Table 5: Five-year progression of diabetic retinopathy - worsening of 2 steps or more on the ETDRS retinopathy severity scale**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Five-year progression of diabetic retinopathy (RR<1 favours more blood pressure control)					
Normotensive at baseline					
5	RCT	6914	Risk Ratio:1.02 [0.92, 1.12]	Moderate	Could not differentiate.
Normotensive at baseline – sensitivity analysis (with the study that does not relate directly to blood pressure control (JEDIT) removed)					
4	RCT	6359	Risk Ratio:0.99 [0.89,1.11]	Moderate	Could not differentiate.
Hypertensive at baseline (RR<1 favours more blood pressure control)					
1	RCT	273	Risk Ratio: 0.62 [0.43, 0.91]	Moderate	Favours more blood pressure control

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121 **Table 6: Five-year Progression to proliferative diabetic retinopathy clinically significant macular oedema, or vitreous haemorrhage**

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Five-year Progression to PDR, CSME, or VH (RR<1 favours more blood pressure control)					
Normotensive at baseline					
2	RCT	3810	Risk Ratio: 1.05 [0.90, 1.21]	High	Could not differentiate.

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**Table 7: Progression of diabetic retinopathy by 7 to 9 years Progression of retinopathy, defined as a two-step or greater progression from baseline on the ETDRS final scale based on evaluation of stereoscopic colour fundus photographs of eyes of participants who had diabetic retinopathy at baseline.**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
7-to-9-year progression of diabetic retinopathy (RR<1 favours more blood pressure control)					
Hypertensive at baseline					
1	RCT	205	Risk Ratio 0.60 [0.43, 0.85]	High	Favours more blood pressure control

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**Table 8: 4-Year Rates of Diabetic Retinopathy Severity Progression: Defined as 3 steps of progression along the ETDRS diabetic retinopathy severity scale.**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Overall (Normotensive at baseline) (RR<1 favours more blood pressure control)					
1	RCT	644	Risk Ratio 0.98 [0.61, 1.58]	Low	Could not differentiate
Subgroup: Microaneurysms or mild DR in 1 eye, no DR or Microaneurysms only in other (Normotensive at baseline)					
1	RCT	370	Risk Ratio: 1.14 [0.44, 2.97]	Low <sup>1</sup>	Could not differentiate
Subgroup: mild/moderate NPDR (Normotensive at baseline) (RR<1 favours more blood pressure control)					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	RCT	194	Risk Ratio:0.64 [0.27, 1.50]	Low	Could not differentiate
Subgroup: moderate/moderately severe NPDR (Normotensive at baseline) (RR<1 favours more blood pressure control)					
1	RCT	80	Risk Ratio 1.31 [0.63, 2.71]	Low	Could not differentiate
1 low quality due to serious risk of bias and indirectness					

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133 **Statins**134 **Table 9: Statins compared to Placebo. Status of Visual Acuity at 18-Week Follow-up (Improved by at least two lines)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Status of Visual Acuity at 18-Week Follow-up (Improved by at least two lines) (RR>1 favours statins)					
2	RCT	80	Risk Ratio 1.86 [0.58, 5.91]	Moderate	Could not differentiate

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136 **Table 10: Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines) by subgroups of with clinically significant macula oedema and without clinically significant macular oedema.**  
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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines) (RR<1 favours statins)					
Overall					
3	RCT	110	Risk Ratio: 0.11 [0.02, 0.58]	Moderate	Favours statins
Clinically significant macular oedema (RR<1 favours statins)					
2	RCT	60	Risk Ratio 0.17 [0.02, 1.31]	Moderate	Could not differentiate
No clinically significant macular oedema (RR<1 favours statins)					
1	RCT	50	Risk Ratio 0.07 [0.00, 1.11]	Moderate	Could not differentiate

138 **Table 11: Macular oedema regression – defined as a resolution or partial resolution of macular oedema.**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Macular oedema regression (RR>1 favours statin)					
2	RCT	60	Risk Ratio: 1.15 [0.49, 2.71]	Low	Could not differentiate
1 >33% of weighted data from studies at moderate or high risk of bias 2 I <sup>2</sup> >33%					

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140 **Table 12: Development of clinically significant macular oedema at 90 days**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Development of CSME at 90 days (RR<1 favours statins)					
1	RCT	50	Risk Ratio: 0.11 [0.01, 1.96]	Moderate	Could not differentiate
1 >33% of weighted data from studies at moderate or high risk of bias 2 Single study					

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**Intensive statin therapy vs standard statin therapy**

148 **Table 13: (ETDRS) DR severity scale- worsening of 2 steps or more on the ETDRS retinopathy severity scale**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
(ETDRS) DR severity scale at 36 months (RR<1 favours statins)					
1 Murakami 2020	RCT	128	Risk Ratio: 0.98 [0.40, 2.37]	Moderate <sup>1</sup>	Could not differentiate
1 Partially applicable Mixed population with 50% population with proliferative disease					

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150 **Table 14: Changes in logMAR VA from baseline to last observation (Best-corrected decimal VA)**

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Changes in logMAR Visual Acuity from baseline to last observation (MD<0 favours statins)					
1 Murakami 2020	RCT	128	MD 0.00 [-0.07, 0.07]	Moderate <sup>1</sup>	Could not differentiate
1 Partially applicable Mixed population with 50% population with proliferative disease					

152 **Fibrates**

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154 **Fenofibrate compared to placebo**

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156 **Table 15: 2-step progression of retinopathy progression of diabetic retinopathy.** This was defined as at least a 2-step increase in ETDRS  
 157 grade after 2 years or more of follow-up for (2-step progression of existing retinopathy in those with a baseline grade of 20 or more) and (2)  
 158 primary (2-step progression to retinopathy in those with a baseline grade of 15 or less).

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Progression of diabetic retinopathy ) (RR<1 favours Fibrates)					
2 (FIELD study, ACCORD EYE study)	RCT	847	Risk Ratio: 0.37 (0.24 to 0.58)	Low	Favours fibrates

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161 **Table 16: Statins plus fenofibrate vs Statin: 4-Year Rates of Diabetic Retinopathy Severity Progression: Defined as 3 steps of**  
 162 **progression along the ETDRS diabetic retinopathy severity scale.**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Overall ) (RR<1 favours fibrates)					
1	RCT	801	Risk Ratio :0.40 [0.24, 0.66]	Low	Favours statins plus fibrate
Subgroup: Microaneurysms or mild DR in 1 eye, no DR or Ma only in other ) (RR<1 favours Fibrates)					
1	RCT	522	Risk Ratio: 0.30 [0.14, 0.65]	Low	Favours statins plus fibrate
Subgroup: mild/moderate NPDR ) (RR<1 favours Fibrates)					
1	RCT	192	Risk Ratio:0.51 [0.20, 1.26]	Low	Could not differentiate

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subgroup: moderate/moderately severe NPDR ) (RR<1 favours Fibrates)					
1	RCT	87	Risk Ratio: 0.51 [0.20, 1.28]	Low	Could not differentiate

163 See [Appendix F](#) for full GRADE tables.



164 **1.1.7 Economic evidence**

165 **1.1.7.1 Included studies.**

166 A single search was performed to identify published economic evaluations of relevance to  
167 any of the questions in this guideline update (see [Appendix B](#)). This search retrieved 672  
168 studies. Based on title and abstract screening, 671 of the studies could confidently be  
169 excluded for this review question. One study was excluded following the full-text review. No  
170 relevant health economic studies were included.

171 **1.1.7.2 Excluded studies**

172 See [Appendix J](#) for excluded studies and reasons for exclusion.

173 See the health economic study selection flow chart presented in [Appendix G](#).

174 **1.1.8 Summary of included economic evidence**

175 No relevant health economic studies were identified to be included.

176 **1.1.9 Economic model**

177 Original health economic modelling was not prioritised for this review question.

178 **1.1.10 The committee's discussion and interpretation of the evidence**

179 **1.1.10.1. The outcomes that matter most**

180 The committee agreed that progression of diabetic retinopathy was an important outcome for  
181 people diagnosed with non-proliferative diabetic retinopathy because proliferative retinopathy  
182 can have very serious consequences if not monitored and treated. Progression by 2 steps on  
183 the Early treatment of Diabetic Retinopathy (ETDRS) severity scale provides a sensitive  
184 measure of progression for non-proliferative retinopathy, where visual acuity is often  
185 unaffected.

186 Visual acuity and macular oedema and were also considered important outcomes as these  
187 outcomes are directly relevant to patients. However, these outcomes were not available for  
188 any of the interventions. The committee were also interested in incidence of macular ischaemia  
189 and health-related quality of life, but these outcomes were not reported for any of the  
190 interventions.

191 The committee wanted to consider if there is a difference in effect by subgroups including  
192 pregnancy, age, and severity of disease. However, the evidence did not stratify the results by  
193 these subgroups.

194 **1.1.10.2. The quality of the evidence**

195 **Blood pressure control**

196 Six studies were identified for people with non-proliferative retinopathy who were eligible for  
197 intensive blood glucose treatment. The evidence for each outcome ranged from moderate to  
198 high quality. Most studies were downgraded for indirectness as a large proportion of

199 participants were people with mild diabetic retinopathy. These people would be treated outside  
 200 of hospital eye services and so are not directly relevant to the scope of this guideline. However,  
 201 the committee agreed that the evidence was still useful.

202 One trial (the JEDIT trial) was an RCT that aimed to investigate the effectiveness of intensive  
 203 glucose-lowering therapy on reducing the risk of diabetic retinopathy in individuals with type 2  
 204 diabetes. The trial was included because it also included intensive blood pressure monitoring  
 205 goals. It reported that the risk of developing diabetic retinopathy was 38% lower in the intensive  
 206 therapy group compared to the standard therapy group. However, the committee noted that  
 207 the intensive glycaemic and lipid lowering targets that were included as part of the intervention  
 208 do not relate directly to blood pressure control. A sensitivity analysis of the results for  
 209 progression was therefore included with this trial removed, but this did not affect the  
 210 interpretation of the effects for blood pressure control-related outcomes (see Figure 2).

211 Two studies (DIRECT Protect 1 & Protect 2) reported combined incidence of proliferative  
 212 diabetic retinopathy, diabetic macular oedema, and vitreous haemorrhages as a single  
 213 outcome, and there was no information on the relative proportions of people with each of these  
 214 individual outcomes. The committee considered this a major limitation because there are  
 215 different pathways for each of these indications, and a composite outcome was not useful for  
 216 decision making. This made it difficult for the committee to make recommendations based on  
 217 these outcomes.

## 218 **Statins**

219 Evidence was available for two comparisons: statins versus placebo (3 RCTs) and intensive  
 220 statin therapy versus standard statin therapy (1 RCT). The evidence for each outcome ranged  
 221 from moderate to low quality, mainly due to studies being at moderate risk of bias because of  
 222 incomplete outcome reporting. The studies were downgraded for indirectness because the  
 223 population included people with mild non-proliferative diabetic retinopathy at the time of  
 224 enrolment. The committee also noted that most studies were on a population with diabetic  
 225 macular oedema as well as non-proliferative diabetic retinopathy. However, they thought this  
 226 evidence could still be used for decision making.

## 227 **Fibrates**

228 Two studies were identified that reported on a subgroup of people with non-proliferative  
 229 diabetic retinopathy at baseline. The ACCORD-Lipid and FIELD studies were two large  
 230 randomized clinical trials that investigated the effect of lipid-lowering therapies on  
 231 cardiovascular outcomes in individuals with type 2 diabetes, but also reported on retinopathy-  
 232 related outcomes. The quality of the evidence for each outcome was low. Evidence was  
 233 downgraded for risk of bias due to selective reporting of outcomes and indirectness, because  
 234 a large proportion of the participants in the subgroup had mild diabetic retinopathy. No  
 235 evidence was available for the other outcomes included in the review protocol.

## 236 **Imprecision and the clinical importance of effects**

237 The committee agreed that for most outcomes, the evidence on blood pressure control  
 238 medicines and fibrates was precise enough to draw conclusions from the evidence. They  
 239 considered that the effects of blood pressure control in the subgroup with hypertension was  
 240 likely to be clinically important. The evidence on statins was from trials with a small number  
 241 of participants, resulting in wide confidence intervals. The committee were therefore limited  
 242 on the conclusions that could be drawn from this evidence.

243 **1.1.10.3 Benefits and harms**244 **Blood pressure control**

245 The ADVANCE study found that intensive glucose control reduced the risk of microvascular  
 246 complications, including diabetic retinopathy, by 21% compared to standard glucose control.  
 247 The study also found that intensive glucose control did not increase the risk of major adverse  
 248 cardiovascular events. The AdRem sub study of the ADVANCE trial found that after 4 years,  
 249 intensive glucose control reduced the risk of progression of diabetic retinopathy by 14%  
 250 compared to standard glucose control. This indicates that intensive glucose control is effective  
 251 in reducing the risk of diabetic retinopathy progression in individuals with type 2 diabetes.  
 252 However, the committee noted that intensive glucose control may be associated with an  
 253 increased risk of hypoglycaemia, which can be a serious adverse event.

254 Of the 6 included studies, 1 study (UKPDS) specifically included people with hypertension at  
 255 baseline. The committee wanted to consider if there is a difference in the effect of blood  
 256 pressure control between subgroups defined by baseline blood pressure. They were aware  
 257 that hypertension was not one of the subgroups in the pre-planned analysis but thought it  
 258 was important to consider this because blood pressure control would be very likely to have  
 259 different effects depending on whether it was elevated at baseline. This subgroup analysis  
 260 was pre-specified in the Cochrane review which was used as a source of evidence for this  
 261 review ([Do et al., 2023](#)). Estimates supported a beneficial effect of blood pressure control  
 262 treatment for people who had hypertension at trial enrolment. There was no clear effect of  
 263 blood pressure control from the studies that included people who were normotensive at  
 264 baseline (see figure 1). The Cochrane review also included a subgroup analysis of  
 265 individuals with type 2 diabetes who had hypertension (see figure 1). The analysis found that  
 266 more intensive blood pressure control, defined as a target systolic blood pressure of less  
 267 than 130 mmHg, reduced the risk of developing diabetic retinopathy compared to less  
 268 intensive blood pressure control, defined as a target systolic blood pressure of less than 140  
 269 mmHg. This finding was consistent with the overall findings of the review.

270 Given that the evidence showed benefits of blood pressure control limiting the progression of  
 271 diabetic retinopathy for people who have hypertension at baseline, the committee thought it  
 272 was important to highlight this in the recommendations. The committee were aware of existing  
 273 recommendations in the [NICE hypertension guideline](#) and noted that most people with  
 274 diabetes and hypertension would be receiving blood pressure control interventions. They  
 275 therefore decided to cross refer to the NICE hypertension guidance, with an additional  
 276 recommendation highlighting the potential benefits of blood pressure control for reducing  
 277 progression of non-proliferative diabetic retinopathy.

278 The committee decided to not include a target blood pressure in the recommendations  
 279 because the quality of evidence for people with hypertension was low and from a single study  
 280 (JEDIT) (see Table 14). It was also noted that this review did not consider the effects of more  
 281 intensive blood pressure control on systemic outcomes and adverse events. The committee  
 282 emphasised it is important to be aware of side effects of antihypertensives, and without further  
 283 evidence they could not make more detailed recommendations.

284 Evidence for people without hypertension at baseline could not differentiate between more  
 285 intensive and less intensive blood pressure control. The committee therefore made a  
 286 recommendation that clinicians should not offer blood pressure control medicines to people  
 287 without hypertension. However, they emphasised that this is only if the blood pressure  
 288 medicine was being prescribed with the aim of reducing progression of non-proliferative  
 289 diabetic retinopathy. If the medicines are being offered for other reasons, then it is important

290 that people are still offered them. The recommendation will ensure that people are not  
291 unnecessarily prescribed medicines that may not provide them with any benefit.

## 292 **Statins**

293 The committee discussed how the evidence suggests that atorvastatin may be an effective  
294 adjunct treatment in the management of people with non-proliferative diabetic retinopathy with  
295 diabetic macular oedema by improving visual acuity and reducing macular oedema. However,  
296 they were concerned about the current limitations of the evidence base, such as the  
297 populations included in the trials. More studies for people with non-proliferative diabetic  
298 retinopathy are therefore needed to show these findings and determine the long-term effects  
299 of atorvastatin treatment in people who have diabetic macular oedema.

300 Most outcomes did not show a clear benefit of statins over placebo. There was some evidence  
301 of a benefit in visual acuity measured at 18 weeks, though most of the studies that reported on  
302 this outcome were from a population who had non-proliferative retinopathy with diabetic  
303 macular oedema or clinically significant macular oedema. Given this limited evidence, the  
304 committee did not think they could make specific recommendations on the use of statins for  
305 diabetic retinopathy. However, they were aware that the [NICE guideline on cardiovascular  
306 disease](#) has recommendations on the use of statins for people with diabetes, and decided it  
307 was important to include a reference to those.

308 The committee noted there is evidence emerging of a possible benefit of statins in groups with  
309 non-proliferative diabetic retinopathy and diabetic macular oedema. Therefore, they decided  
310 to make a research recommendation into the effectiveness of intensive statin treatment  
311 compared with standard statin treatment for this group (see [Appendix K](#)).

312 An additional issue identified by the committee is the limited research on the use of statins for  
313 people from ethnic minority backgrounds who have diabetic retinopathy. The committee were  
314 aware there is evidence from large-scale clinical trials that statins can be effective in reducing  
315 the risk of cardiovascular disease in populations with diabetes, including those from ethnic  
316 minority backgrounds. Similar research is needed to better understand the potential benefits  
317 of statin therapy in people from ethnic minority backgrounds with diabetic retinopathy. People  
318 of different ethnicities were therefore included as a subgroup in the intensive statin therapy  
319 research recommendation (see [Appendix K](#)).

## 320 **Fibrates**

321 Two studies (the ACCORD-Lipid study and the FIELD study) were designed to investigate  
322 whether intensive lipid-lowering therapy with a combination of a statin and a fibrate would  
323 reduce the risk of cardiovascular events in individuals with type 2 diabetes who were at high  
324 risk for cardiovascular disease. Although, intensive lipid-lowering therapy with the combination  
325 of a statin and a fibrate did not reduce the risk of major cardiovascular events, a post-hoc  
326 analysis of the ACCORD-Lipid study found that in people with advanced stages of retinopathy  
327 it did reduce the risk of diabetic retinopathy progression by 40% compared to standard lipid-  
328 lowering therapy with a statin alone. The FIELD Eye study showed benefits of fibrates,  
329 reducing the risk of progression of diabetic retinopathy by 30% and reducing the need for laser  
330 treatment for diabetic retinopathy by 31% compared to placebo.

331 The committee also reviewed evidence from the ACCORD study stratified by severity of  
332 retinopathy at baseline. The evidence showed that for the subgroup of people with very mild  
333 diabetic retinopathy, fibrate slowed progression of retinopathy at 5 years. Similarly, for people  
334 with mild or moderate and moderate to moderately severe non-proliferative diabetic  
335 retinopathy, the overall effect showed a benefit of fibrates on reducing progression of

336 retinopathy, however, the committee were in agreement that the wider confidence intervals  
337 could be due to the small numbers in these groups and there was no evidence of a difference  
338 across subgroups. The FIELD Eye study demonstrated that treatment with fibrate was effective  
339 in reducing the risk of progression of diabetic retinopathy and the need for laser treatment for  
340 diabetic retinopathy.

341 The committee agreed that both studies provide valuable insights into the potential benefits of  
342 lipid-lowering therapies for the management of diabetic retinopathy in individuals with type 2  
343 diabetes and so they decided to recommend the use of fibrates for people with non-proliferative  
344 diabetic retinopathy and type 2 diabetes. The majority of the evidence was for people with type  
345 2 diabetes, and the committee did not think they could extrapolate this information to people  
346 who have type 1 diabetes. However, they were aware of an ongoing clinical trial for the use of  
347 fibrates for people with type 1 diabetes which could be used to make recommendations in the  
348 future.

349 The committee discussed the lack of evidence on the effects of fibrates for pregnant women  
350 and for people of different ethnicities who are at high risk of developing diabetes and diabetic  
351 retinopathy. They therefore added fibrates to the research recommendation about people of  
352 different ethnic backgrounds (see [Appendix K](#)).

#### 353 **1.1.10.4 Cost effectiveness and resource use**

354 No relevant economic evaluations were identified which addressed the cost effectiveness of  
355 lipid modification therapies and antihypertensive medicines. Overall, the committee were not  
356 concerned of any resource impact from the recommendations for blood pressure control and  
357 statins because they are recommending the continuation of current practice. The committee  
358 acknowledged the increased use of fibrates could have a resource impact; however, the  
359 committee chose to restrict the population to those with type 2 diabetes based on the  
360 evidence base to ensure any potential resource impact would be limited.

#### 361 **Blood pressure control**

362 No resource impact is expected by the committee because the recommendations are based  
363 on the existing NICE guidance for hypertension.

#### 364 **Statins**

365 No resource impact is expected because the recommendations are based on the existing  
366 NICE guidance for cardiovascular disease: risk assessment and reduction, including lipid  
367 modification guideline.

#### 368 **Fibrates**

369 The committee considered the resource impact associated with recommending fenofibrates  
370 to people with non-proliferative diabetic retinopathy and acknowledged that the increased  
371 use of fibrates could have a resource impact, however from the evidence would expect the  
372 clinical benefits and potential future cost savings by reducing progression to outweigh the  
373 upfront costs. The committee noted that the evidence for the benefit of fibrates was limited  
374 and restricted to people with type 2 diabetes and therefore decided to only use a consider  
375 recommendation restricted to people with type 2 diabetes. This was based on the population  
376 which the evidence is based on to limit any resource implications until further research has  
377 been undertaken on the benefits of fibrates in people with non-proliferative diabetic  
378 retinopathy with type 1 diabetes.

379 **1.1.10.5 Other factors the committee took into account.**

380 The committee also discussed the impact of socioeconomic status on the ability to benefit from  
381 the interventions discussed. They noted the association between lower socioeconomic status  
382 and poorer outcomes in people with diabetic retinopathy. They noted that prescription costs  
383 could be a barrier to taking a regular medicine like fibrates. However, people who are receiving  
384 medicines for type 2 diabetes should receive free prescriptions, which will mitigate this problem  
385 if they are made aware of this and apply for a medical exemption certificate.

386 **1.1.11 Recommendations supported by this evidence review**

387 This evidence review supports Recommendations 1.1.6 to 1.1.10 and the research  
388 recommendations on intensive statin therapy for people with non-proliferative retinopathy  
389 and diabetic macular oedema and fibrates for the prevention of progression of diabetic  
390 retinopathy in people with different ethnicities.

391 **1.1.12 References – included studies**

392 **1.1.12.1 Clinical evidence – systematic reviews**

393 [Do et al. \(2023\)](#). Do DV, Han G, Abariga SA, Sleilati G, Vedula SS, Hawkins BS. Blood  
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396 Ltd.

397 [Kataoka et al \(2023\)](#). Kataoka SY, Lois N, Kawano S, Kataoka Y, Inoue K, Watanabe N.  
398 Fenofibrate for diabetic retinopathy. Cochrane Database of Systematic Reviews 2023, Issue  
399 6.

400 **1.1.12.1 Clinical evidence – primary studies**

401 Multiple studies were reported from each trial in the Cochrane reviews. The full list of studies  
402 are provided under each trial name.

403 **Included studies from Antihypertensives Cochrane review:** [Do et al 2023](#)

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406 Group and Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION)  
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- 419 ADVANCE Management Committee. Study rationale and design of ADVANCE: Action in  
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# Appendices

## Appendix A – Review protocol

**Review protocol for the effectiveness of lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy.**

ID	Field	Content
0.	PROSPERO registration number	This protocol was not registered with PROSPERO
1.	Review title	The effectiveness of lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy
2.	Review question	What is the effectiveness of lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy
3.	Objective	<p>To determine the clinical and cost effectiveness of different therapies including lipid modification therapies and antihypertensive medicines to reduce the risk of progression of non-proliferative diabetic retinopathy.</p> <p>Two Cochrane reviews have been identified which partially cover this question:</p> <p><a href="https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy">https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy</a></p>

		<p><a href="https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full">https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full</a></p> <p>These reviews are being updated by Cochrane alongside development of the NICE guideline on diabetic retinopathy and will be used directly as evidence to answer this review question. The Cochrane reviews cover a broader population than the scope of this guideline (people with diabetes who do and do not have diabetic retinopathy), so only a subset of the studies included in the Cochrane review will be used in this evidence review.</p> <p>The committee identified statins as another lipid modification therapy that should be considered. This aspect of the review will be addressed by a new systematic review which is described in this protocol.</p>
4.	Searches	<p>Studies from the following Cochrane reviews will be considered for inclusion:</p> <p><a href="https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy">https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy</a></p> <p><a href="https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full">https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full</a></p>

		<p>A systematic search will be conducted to cover the fibrates other than fenofibrates and statins , which are not covered by existing Cochrane reviews:</p> <p>The following databases will be searched for the clinical review:</p> <ul style="list-style-type: none"><li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li><li>• Cochrane Database of Systematic Reviews (CDSR)</li><li>• Embase</li><li>• Epistemonikos</li><li>• HTA (legacy records)</li><li>• INAHTA</li><li>• MEDLINE</li><li>• Medline in Process</li><li>• Medline EPub Ahead of Print</li></ul> <p>For the economics review the following databases will be searched on population only:</p> <ul style="list-style-type: none"><li>• Embase</li><li>• MEDLINE</li><li>• Medline in Process</li><li>• Medline EPub Ahead of Print</li><li>• Econlit</li><li>• HTA (legacy records)</li><li>• NHS EED (legacy records)</li><li>• INAHTA</li></ul>
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		<p>Searches will be restricted by:</p> <ul style="list-style-type: none"> <li>• Studies reported in English</li> <li>• Study design RCT will be applied</li> <li>• Animal studies will be excluded from the search results</li> <li>• Conference abstracts will be excluded from the search results</li> </ul> <ul style="list-style-type: none"> <li>• No date limit will be set unless specified by the protocol</li> <li>• Cost Utility (specific) and Cohort Studies for the economic search</li> </ul> <p>Other searches:</p> <ul style="list-style-type: none"> <li>• None identified</li> </ul> <p>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.</p> <p>The full search strategies for all databases will be published in the final review.</p>
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	<p>Inclusion:</p> <p>People diagnosed with non-proliferative diabetic retinopathy</p>

		<p>Studies with mixed populations, where the remaining people in the population are people with type 2 diabetes but no diabetic retinopathy or people with proliferative diabetic retinopathy will be included if more than 50% meet the inclusion criteria.</p>
7.	Intervention	<p>Blood pressure control interventions (as described in Cochrane review):</p> <ul style="list-style-type: none"> <li>• Strict blood pressure control, alone or in combination with other interventions, when compared with less strict blood pressure control</li> <li>• Any blood pressure control, when compared with placebo</li> <li>• Any class of anti-hypertensive medicine compared with another class of anti-hypertensive medicine</li> </ul> <p>Fibrates (limited to those with a UK marketing authorisation):</p> <ul style="list-style-type: none"> <li>• Bezafibrate, ciprofibrate, gemfibrozil</li> <li>• Fenofibrate (as described in Cochrane review): (any dose/regimen)</li> </ul> <p>Statins:</p> <ul style="list-style-type: none"> <li>• Statin medications (for example atorvastatin, simvastatin)</li> <li>• Statins in combination with another lipid modification therapy or antihypertensive medication.</li> </ul>
8.	Comparator	<p>Blood pressure control interventions (as described in Cochrane review):</p> <ul style="list-style-type: none"> <li>– Less strict blood pressure control when compared with strict blood pressure control</li> <li>– Placebo</li> <li>– Another class of anti-hypertensive medicine when compared with a class of anti-hypertensive medicine</li> </ul>

		<p>Fibrates =</p> <ul style="list-style-type: none"> <li>– Placebo or observation (no treatment)</li> </ul> <p>Statins:</p> <ul style="list-style-type: none"> <li>– Fibrate (any dose/regimen)</li> <li>– Any blood pressure control intervention</li> <li>– Placebo or observation (no treatment)</li> </ul>
9.	Types of study to be included	Randomised controlled trials
10.	Other exclusion criteria	<p>Trials that were not reported in English will not be included if identified by the systematic search (trials not reported in English that have been obtained and the data extracted as part of the Cochrane reviews will be included).</p> <p>Studies comparing different doses of medicines only will be excluded.</p>
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom.
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> <li>• Progression of diabetic retinopathy (defined as advancing two or more steps in the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, based on evaluation of stereoscopic or non-stereoscopic colour fundus photograph)</li> </ul>

13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> <li>• Visual acuity             <ul style="list-style-type: none"> <li>○ For blood pressure control interventions (Cochrane review), reported as proportion with reduction of visual acuity by three or more lines in both eyes on a logMAR chart</li> <li>○ For fenofibrate (Cochrane review) reported as mean visual acuity and proportion of participants with a reduction in visual acuity of 10 ETDRS letters or more (equivalent to 2 or more lines on a logMAR chart)</li> <li>○ For statins and other fibrates (original review), reported as mean visual acuity or proportion participants with a reduction in visual acuity of 2 or 3 lines on a logMAR chart, as reported by the studies.</li> </ul> </li> <li>• Incidence of proliferative diabetic retinopathy</li> <li>• Incidence of diabetic macular oedema</li> <li>• Incidence of diabetic macular ischaemia</li> <li>• Vision related quality of life (measured using validated tool)</li> </ul> <p><b>Applies to primary and secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Outcomes will be reported at the latest time point reported by the study.</li> <li>• As the review is investigating the effectiveness of systematic treatments, the unit of analysis will be the individual participant.</li> <li>• Where results for 2 eyes from the same participant these will be ideally adjust for the within person correlation. Results from such studies will be incorporated using the generic inverse variance function in RevMan 5. Studies that have not accounted for the within person correlation will be incorporated and the implications of this on the interpretation will be considered.</li> </ul>



14.	Data extraction (selection and coding)	<p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.</p> <p>Evidence tables created as part of the Cochrane reviews that are used as a source of studies for this review will be used without modification.</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using appropriate checklists as described in <a href="#">Developing NICE guidelines: the manual</a>.</p> <p>Risk of bias in RCTs will be assessed using the <a href="#">Cochrane risk of bias version 2 tool</a>.</p> <p>Risk of bias judgments made as part of the Cochrane reviews that are used as a source of studies for this review will be used without modification.</p>
16.	Strategy for data synthesis	<p>Network meta-analysis will not be conducted for this review as the aim is not to identify the best treatment in a range of alternatives.</p>

		<p>Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event.</p> <p>A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g).</p> <p>Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as <math>I^2 \geq 50\%</math>, when random effects models will be used instead.</p> <p>A modified version of GRADE will be used to assess the quality of the outcomes (GRADE judgements made as part of the Cochrane reviews will not be used, as not all of the trials included in the Cochrane review are included in this review). Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee discussion section of the evidence review. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.</p>
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17.	Analysis of sub-groups	<p>Dose of medication will not be included as a subgroup analysis because doses are likely to be individualised for each participant according to their lipid and blood pressure profile. Instead, the doses used in the studies will be presented to the committee alongside the analysis for their consideration.</p> <p>Data will be presented separately for the following groups:</p> <ul style="list-style-type: none"> <li>• Pregnant women</li> </ul> <p>If data is available a subgroup analysis will be conducted by:</p> <ul style="list-style-type: none"> <li>• Ethnicity</li> <li>• People with a learning disability</li> <li>• Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80)</li> <li>• Socioeconomic status</li> <li>• Type 1 diabetes vs type 2 diabetes</li> </ul>												
18.	Type and method of review	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center; width: 10%;"><input checked="" type="checkbox"/></td> <td style="width: 10%;"></td> <td style="width: 80%;">Intervention</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td></td> <td>Diagnostic</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td></td> <td>Prognostic</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td></td> <td>Qualitative</td> </tr> </table>	<input checked="" type="checkbox"/>		Intervention	<input type="checkbox"/>		Diagnostic	<input type="checkbox"/>		Prognostic	<input type="checkbox"/>		Qualitative
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		<input type="checkbox"/> Epidemiologic <input type="checkbox"/> Service Delivery <input type="checkbox"/> Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	<b>Review stage</b>	<b>Started</b>	<b>Completed</b>
		Preliminary searches	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>

		Formal screening of search results against eligibility criteria	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
		Data extraction	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
		Data analysis	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
24.	Named contact	<p><b>5a. Named contact</b> NICE Guideline Development Team</p> <p><b>5b Named contact e-mail</b> <a href="mailto:diabeticretinopathy@nice.org.uk">diabeticretinopathy@nice.org.uk</a></p> <p><b>5e Organisational affiliation of the review</b> National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team</p>		
25.	Review team members	<p>From the Guideline development team:</p> <ul style="list-style-type: none"> <li>• Kathryn Hopkins</li> </ul>		

		<ul style="list-style-type: none"> <li>• Ahmed Yosef</li> <li>• Syed Mohiuddin Hannah Lomax</li> <li>• Kirsty Hounsell</li> <li>• Jenny Craven</li> <li>• Jenny Kendrick</li> </ul>
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline development team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website: <a href="https://www.nice.org.uk/guidance/indevelopment/gid-ng10160">https://www.nice.org.uk/guidance/indevelopment/gid-ng10160</a>
29.	Other registration details	None

30.	Reference/URL for published protocol	None
31.	Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> <li>• notifying registered stakeholders of publication</li> <li>• publicising the guideline through NICE's newsletter and alerts</li> <li>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.</li> </ul>
32.	Keywords	Diabetic retinopathy, blood pressure control, fenofibrates, statins
33.	Details of existing review of same topic by same authors	None
34.	Current review status	<input checked="" type="checkbox"/> Ongoing <input type="checkbox"/> Completed but not published <input type="checkbox"/> Completed and published <input type="checkbox"/> Completed, published and being updated <input type="checkbox"/> Discontinued
35..	Additional information	None

36.	Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>
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## Appendix B – Literature search strategies

### Search design and peer review

NICE information specialists conducted the literature searches for the evidence review. The searches were run in June 2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

### Review Management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

### Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, conference abstract or conference paper or "conference review" were applied in adherence to standard NICE practice and the review protocol. The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

### Search filters

The following search filters were applied to the clinical searches in MEDLINE and Embase to identify:

#### RCTs

The MEDLINE RCT filter was [McMaster Therapy – Medline - "best balance of sensitivity and specificity" version](#). The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.

The Embase RCT filter was [McMaster Therapy – Embase “best balance of sensitivity and specificity” version](#).

## ***Clinical search strategies***

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	20/06/2022	Wiley	Issue 5 of 12, May 2022
Cochrane Database of Systematic Reviews (CDSR)	20/06/2022	Wiley	Issue 6 of 12, June 2022
Embase	20/06/2022	Ovid	1974 to 2022 June 17
Epistemonikos	20/06/2022	N/A	Search run on 20 June 2022
HTA	20/06/2022	CRD	Search run on 20 June 2022
INAHTA	20/06/2022	N/A	Search run on 20 June 2022
MEDLINE	20/06/2022	Ovid	1946 to June 17, 2022
MEDLINE-in-Process	20/06/2022	Ovid	1946 to June 17, 2022
MEDLINE ePub Ahead-of-Print	20/06/2022	Ovid	June 17, 2022

<b>Database:</b> Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)			
#1	MeSH descriptor: [Diabetic Retinopathy] explode all trees	1575	
#2	MeSH descriptor: [Macular Edema] explode all trees	1274	
#3	((diabet* near/6 (retin* or eye* or macular* or maculopath*)))	5557	ti,ab,kw
#4	#1 or #2 or #3	5998	
#5	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	3716	
#6	MeSH descriptor: [Atorvastatin] this term only	1844	
#7	MeSH descriptor: [Simvastatin] this term only	1837	
#8	MeSH descriptor: [Fluvastatin] this term only	331	
#9	MeSH descriptor: [Pravastatin] explode all trees	1023	
#10	MeSH descriptor: [Rosuvastatin Calcium] this term only	1173	
#11	((atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluidostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*)):ti,ab,kw	12334	
#12	((hmgcoa reductase* or hmg-coa reductase*) near/4 inhibitor*)):ti,ab,kw	6628	

#13	((hydroxymethylglutary* near/4 inhibitor*)):ti,ab,kw	5192
#14	(statin*):ti,ab,kw	10653
#15	{or #5-#14}	19597
#16	MeSH descriptor: [Bezafibrate] this term only	235
#17	((Bezafibrate* or Fibrazate*)):ti,ab,kw	465
#18	((ciprofibrate* or lipanor*)):ti,ab,kw	44
#19	MeSH descriptor: [Gemfibrozil] this term only	326
#20	((gemfibrozil* or lopid*)):ti,ab,kw	560
#21	{or #16-#20}	1019
#22	#15 or #21	20342
#23	#4 and #22	97

<b>Database:</b> Embase		
1	diabetic retinopathy/	46724
2	macular edema/	6174
3	(diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw.	51713
4	1 or 2 or 3	70190
5	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/	177217
6	Statin*.tw.	80425
7	atorvastatin/ or simvastatin/ or flindostatin/ or pravastatin/ or rosuvastatin/	84101
8	(atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or flindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw.	41672
9	((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*).tw.	6510
10	(hydroxymethylglutary* adj4 inhibitor*).tw.	545
11	or/5-10	197339
12	bezafibrate/	5562
13	(Bezafibrate* or Fibrazate*).tw.	2203
14	ciprofibrate/	1357
15	(ciprofibrate* or lipanor*).tw.	625
16	gemfibrozil/	9131
17	(gemfibrozil* or lopid*).tw.	2905
18	or/12-17	13818
19	11 or 18	204787
20	4 and 19	1418
21	Nonhuman/ not Human/	5021210
22	20 not 21	1388
23	limit 22 to english language	1324
24	random:.tw.	1816185
25	placebo:.mp.	499377
26	double-blind:.tw.	232197
27	or/24-26	2085315
28	23 and 27	286
29	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5242410
30	28 not 29	259

**Database: Epistemonikos**

(title:(Diabetic retinopath\* OR macular edema OR macular oedema OR diabetic maculopath\*) OR abstract:(Diabetic retinopath\* OR macular edema OR macular oedema OR diabetic maculopath\*))

AND

(title:(Statin\* OR atorvastatin\* OR lipitor\* OR simvastatin\* OR zocor\* OR fluvastatin\* OR fluindostatin\* OR lescol\* OR pravastatin\* OR lipostat\* OR rosuvastatin\* OR crestor\* OR dorisin\* OR nandovar\* OR hmgcoa reductase\* OR hmg-coa reductase\* OR hydroxymethylglutary\*) OR abstract:(Statin\* OR atorvastatin\* OR lipitor\* OR simvastatin\* OR zocor\* OR fluvastatin\* OR fluindostatin\* OR lescol\* OR pravastatin\* OR lipostat\* OR rosuvastatin\* OR crestor\* OR dorisin\* OR nandovar\* OR hmgcoa reductase\* OR hmg-coa reductase\* OR hydroxymethylglutary\*))

OR

(title:(ciprofibrate\* OR lipanor\*) OR abstract:(ciprofibrate\* OR lipanor\*)) OR (title:(gemfibrozil\* OR lopic\*) OR abstract:(gemfibrozil\* OR lopic\*)) OR (title:(Bezafibrate\* OR Fibrazate\*) OR abstract:(Bezafibrate\* OR Fibrazate\*))

**Database: Health Technology Assessment (HTA)**

Search	Hits	
1	(MeSH DESCRIPTOR diabetic retinopathy IN HTA)	29
2	(MeSH DESCRIPTOR macular edema IN HTA)	25
3	((diabet* NEAR/4 (retin* or eye* or macular* or maculopath*)) IN HTA)	60
4	#1 OR #2 OR #3	67
5	(MeSH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors EXPLODE ALL TREES IN HTA)	23
6	((Statin*) IN HTA)	59
7	(MeSH DESCRIPTOR Atorvastatin IN HTA)	0
8	(MeSH DESCRIPTOR Simvastatin IN HTA)	3
9	(MeSH DESCRIPTOR Fluvastatin IN HTA)	0
10	(MeSH DESCRIPTOR Pravastatin IN HTA)	1
11	(MeSH DESCRIPTOR Rosuvastatin Calcium IN HTA)	0

12	((atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*) IN HTA)	17
13	(((((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*)) IN HTA)	4
14	((((hydroxymethylglutary* NEAR/4 inhibitor*)) IN HTA)	21
15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	69
16	(MeSH DESCRIPTOR Bezafibrate IN HTA)	0
17	((((Bezafibrate* or Fibrazate*)) IN HTA)	0
18	((((ciprofibrate* or lipanor*)) IN HTA)	0
19	(MeSH DESCRIPTOR Gemfibrozil IN HTA)	0
20	((((gemfibrozil* or lopid*)) IN HTA)	0
21	#16 OR #17 OR #18 OR #19 OR #20	0
22	#15 OR #21	69
23	#4 AND #22	0

**Database:** International Network of Agencies for Health Technology Assessment (INAHTA)

19	#17 OR #18	
18	#16 AND #4	0
17	#15 AND #4	0
16	((("Gemfibrozil"[mh]) OR ("Bezafibrate"[mh]) OR (Bezafibrate* OR Fibrazate*) OR (gemfibrozil* OR lopid*) OR (ciprofibrate* OR lipanor*))	
15	#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	93
14	(hydroxymethylglutary* AND inhibitor*)	0
13	((hmgcoa reductase* or hmg-coa reductase*) AND inhibitor*)	10
12	atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*	16
11	"Rosuvastatin Calcium"[mh]	0
10	"Pravastatin"[mh]	1
9	"Fluvastatin"[mh]	0
8	"Simvastatin"[mh]	5
7	"Atorvastatin"[mh]	1
6	Statin*	75
5	"Hydroxymethylglutaryl-CoA Reductase Inhibitors"[mh]	27
4	#3 OR #2 OR #1	94
3	(diabet* AND (retin* or eye* or macular* or maculopath*))	86

2	"Macular Edema"[mh]	27
1	"Diabetic Retinopathy"[mh]	40

**Database: Ovid MEDLINE(R)**

1	Diabetic Retinopathy/	28299
2	Macular Edema/	8494
3	(diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw.	32726
4	1 or 2 or 3	42961
5	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	45143
6	Statin*.tw.	43227
7	Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/	20022
8	(atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or flindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw.	21890
9	((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*).tw.	4433
10	(hydroxymethylglutary* adj4 inhibitor*).tw.	460
11	or/5-10	65284
12	Bezafibrate/	1260
13	(Bezafibrate* or Fibrazate*).tw.	1556
14	(ciprofibrate* or lipanor*).tw.	475
15	Gemfibrozil/	1401
16	(gemfibrozil* or lipid*).tw.	1839
17	or/12-16	4089
18	11 or 17	68519
19	4 and 18	229
20	Animals/ not Humans/	5006645
21	19 not 20	206
22	limit 21 to english language	192
23	randomized controlled trial.pt.	575357
24	randomi?ed.mp.	928917
25	placebo.mp.	218867
26	or/23-25	985080
27	22 and 26	56

**Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations**

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw.	5
4	1 or 2 or 3	5
5	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	0
6	Statin*.tw.	6
7	Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/	0

8	(atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw.	2
9	((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*).tw.	0
10	(hydroxymethylglutary* adj4 inhibitor*).tw.	0
11	or/5-10	7
12	Bezafibrate/	0
13	(Bezafibrate* or Fibrazate*).tw.	1
14	(ciprofibrate* or lipanor*).tw.	0
15	Gemfibrozil/	0
16	(gemfibrozil* or lopid*).tw.	0
17	or/12-16	1
18	11 or 17	8
19	4 and 18	0
20	Animals/ not Humans/	0
21	19 not 20	0
22	limit 21 to english language	0

**Database: Ovid MEDLINE(R) Epub Ahead of Print**

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw.	518
4	1 or 2 or 3	518
5	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	0
6	Statin*.tw.	700
7	Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/	0
8	(atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw.	221
9	((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*).tw.	34
10	(hydroxymethylglutary* adj4 inhibitor*).tw.	5
11	or/5-10	841
12	Bezafibrate/	0
13	(Bezafibrate* or Fibrazate*).tw.	5
14	(ciprofibrate* or lipanor*).tw.	0
15	Gemfibrozil/	0
16	(gemfibrozil* or lopid*).tw.	15
17	or/12-16	20
18	11 or 17	857
19	4 and 18	2
20	Animals/ not Humans/	0
21	19 not 20	2
22	limit 21 to english language	2

## **Cost effectiveness searches**

A broad search covering the diabetic retinopathy population was used to identify studies on cost effectiveness. The searches were run in February 2022.

## **Limits and restrictions**

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, comment or letter or editorial or historical articles or conference abstract or conference paper or "conference review" or letter or case report were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

## **Search filters**

### **Cost utility**

The NICE cost utility filter was applied to the search strategies in MEDLINE and Embase to identify cost-utility studies.

Hubbard W, et al. Development of a validated search filter to identify cost utility studies for NICE economic evidence reviews. NICE Information Services.

### **Cohort studies**

For the modelling, cohort/registry terms were used from the NICE observational filter that was developed in-house.

The NICE Organisation for Economic Co-operation and Development (OECD) filter was also applied to search strategies in MEDLINE and Embase.

Ayiku, L., Hudson, T., et al (2021) [The NICE OECD countries geographic search filters: Part 2 – Validation of the MEDLINE and Embase \(Ovid\) filters](#). *Journal of the Medical Library Association*)

## **Cost effectiveness search strategies**

<b>Database</b>	<b>Date searched</b>	<b>Database Platform</b>	<b>Database segment or version</b>
EconLit	16/02/2022	OVID	<1886 to February 13, 2022>



Embase (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1974 to 2022 February 16>
HTA	16/02/2022	CRD	16-Feb-2022
INAHTA	16/02/2022	INAHTA	16-Feb-2022
MEDLINE (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE-in-Process (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE Epub Ahead-of-Print (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<February 16, 2022>
NHS EED	16/02/2022	CRD	N/A

**Database: EconLit**

- 1 Diabetic Retinopathy/ 0
- 2 Macular Edema/ 0
- 3 (diabet\* adj4 (retin\* or eye\* or macular\*)).tw. 14
- 4 1 or 2 or 3 14

**Database: Embase**

Cost utility search:

- 1 diabetic retinopathy/ 45217
- 2 macular edema/ 5687
- 3 (diabet\* adj4 (retin\* or eye\* or macular\*)).tw. 47443
- 4 1 or 2 or 3 65931
- 5 cost utility analysis/ 10912
- 6 (cost\* and ((qualit\* adj2 adjust\* adj2 life\*) or qaly\*)).tw. 26154
- 7 ((incremental\* adj2 cost\*) or ICER).tw. 26757
- 8 (cost adj2 utilit\*).tw. 9655
- 9 (cost\* and ((net adj benefit\*) or (net adj monetary adj benefit\*) or (net adj health adj benefit\*))).tw. 2715
- 10 ((cost adj2 (effect\* or utilit\*)) and (quality adj of adj life)).tw. 31906
- 11 (cost and (effect\* or utilit\*)).ti. 51363
- 12 or/5-11 81030
- 13 4 and 12 417
- 14 nonhuman/ not human/ 4929899
- 15 13 not 14 415
- 16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583

17 15 not 16 302

## Cohort studies:

1 diabetic Retinopathy/ 45440  
2 macular Edema/ 5828  
3 (diabet\* adj4 (retin\* or eye\* or macular\*)).tw. 47762  
4 or/1-3 66388  
5 cohort analysis/ 811098  
6 Retrospective study/ 1206857  
7 Prospective study/ 748103  
8 (Cohort adj (study or studies)).tw. 380594  
9 (cohort adj (analy\* or regist\*)).tw. 16437  
10 (follow up adj (study or studies)).tw. 68508  
11 longitudinal.tw. 384899  
12 prospective.tw. 981024  
13 retrospective.tw. 1068301  
14 or/5-13 3358085  
15 4 and 14 13743  
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/  
or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp  
azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or  
belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/  
or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or  
burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central  
african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or  
cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or  
djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or  
equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of  
micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or  
grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or  
honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/  
or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or  
lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or  
madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or  
mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or  
"montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or  
nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/  
or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or  
paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north  
macedonia"/ or romania/ or exp russian federation/ or rwanada/ or sahel/ or "saint  
kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi  
arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or  
"sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or  
south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or  
suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or

timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/  
 or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or  
 exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or  
 yemen/ or zambia/ or zimbabwe/ 1511773

17 exp "organisation for economic co-operation and development"/ 1933

18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or  
 exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/  
 or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or  
 greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/  
 or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new  
 zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or  
 scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or  
 switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or  
 western europe/ 3545238

19 european union/ 29144

20 developed country/ 34415

21 or/17-20 3576072

22 16 not 21 1373176

23 15 not 22 12938

24 limit 23 to english language 12133

25 nonhuman/ not human/ 4938000

26 24 not 25 12067

27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract  
 or conference paper or "conference review" or letter or editorial or case report).pt.  
 7072757

28 26 not 27 8733

29 limit 28 to dc=20120101-20220228 6467

**Database:** Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118

2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82

3 ((diabet\* adj4 (retin\* or eye\* or macular\*))) 216

4 #1 OR #2 OR #3 245

5 \* IN HTA FROM 2012 TO 2022 5598

6 #4 AND #5 26

**Database:** International Network of Agencies for Health Technology Assessment (INAHTA)

6 #5 AND #4 47

5 \* FROM 2012 TO 2022 7610

4	#3 OR #2 OR #1	92	
3	((diabet* AND (retin* or eye* or macular*)))		84
2	"Macular Edema"[mh]	27	
1	"Diabetic Retinopathy"[mh]	39	

**Database:** Ovid MEDLINE(R)

## Cost utility search:

1	Diabetic Retinopathy/	27250	
2	Macular Edema/	8126	
3	(diabet* adj4 (retin* or eye* or macular*)).tw.		29608
4	1 or 2 or 3	40314	
5	Cost-Benefit Analysis/	88398	
6	(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.		13197
7	((incremental* adj2 cost*) or ICER).tw.		13599
8	(cost adj2 utilit*).tw.	5176	
9	(cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.	1698	
10	((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.		17986
11	(cost and (effect* or utilit*)).ti.	30223	
12	or/5-11	100083	
13	4 and 12	287	
14	animals/ not humans/	4924997	
15	13 not 14	287	

## Cohort studies:

1	Diabetic Retinopathy/	27317	
2	Macular Edema/	8133	
3	(diabet* adj4 (retin* or eye* or macular*)).tw.		29694
4	or/1-3	40407	
5	exp Cohort Studies/	2302163	
6	(cohort adj (study or studies)).tw.	225137	
7	(cohort adj (analy* or regist*)).tw.	8773	
8	(follow up adj (study or studies)).tw.		48799
9	longitudinal.tw.	243228	
10	prospective.tw.	570236	
11	retrospective.tw.	546033	
12	or/5-11	2652900	
13	4 and 12	10289	
14	afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/		

or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanada/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1201994

15 "organisation for economic co-operation and development"/ 417

16 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3386234

17 european union/ 17116

18 developed countries/ 21089

19 or/15-18 3401513

20 14 not 19 1115138

21 13 not 20 9710

22 limit 21 to english language 8875

23 Animals/ not Humans/ 4930479

24 22 not 23 8825

25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2225022

26	24 not 25	8658	
27	limit 26 to ed=20120101-20220228		4813

**Database:** Ovid MEDLINE(R) In-Process & In-Data-Review Citations

## Cost utility search:

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	335
4	1 or 2 or 3	335
5	Cost-Benefit Analysis/	0
6	(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.	196
7	((incremental* adj2 cost*) or ICER).tw.	177
8	(cost adj2 utilit*).tw.	74
9	(cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.	29
10	((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.	242
11	(cost and (effect* or utilit*)).ti.	286
12	or/5-11	450
13	4 and 12	2
14	animals/ not humans/	0
15	13 not 14	2

## Cohort studies:

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	336
4	or/1-3	336
5	exp Cohort Studies/	0
6	(cohort adj (study or studies)).tw.	4157
7	(cohort adj (analy* or regist*)).tw.	155
8	(follow up adj (study or studies)).tw.	263
9	longitudinal.tw.	3119
10	prospective.tw.	5190
11	retrospective.tw.	6965
12	or/5-11	15689
13	4 and 12	71
14	limit 13 to english language	71
15	limit 14 to dt=20120101-20220228	70

**Database:** Ovid MEDLINE(R) Epub Ahead of Print

## Cost utility search:

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	585
4	1 or 2 or 3	585
5	Cost-Benefit Analysis/	0
6	(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.	459
7	((incremental* adj2 cost*) or ICER).tw.	395
8	(cost adj2 utilit*).tw.	195
9	(cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.	59
10	((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.	625
11	(cost and (effect* or utilit*)).ti.	615
12	or/5-11	1199
13	4 and 12	9
14	animals/ not humans/	0
15	13 not 14	9

## Cohort studies:

1	Diabetic Retinopathy/	0
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	563
4	or/1-3	563
5	exp Cohort Studies/	0
6	(cohort adj (study or studies)).tw.	9207
7	(cohort adj (analy* or regist*)).tw.	349
8	(follow up adj (study or studies)).tw.	607
9	longitudinal.tw.	6722
10	prospective.tw.	12241
11	retrospective.tw.	18324
12	or/5-11	37987
13	4 and 12	147
14	limit 13 to english language	147

**Database:** NHS Economic Evaluation Database

1	MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES	118
2	MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES	82
3	((diabet* adj4 (retin* or eye* or macular*)))	216
4	#1 OR #2 OR #3	245
5	* IN NHSEED FROM 2012 TO 2022	4897

6 #4 AND #5 19



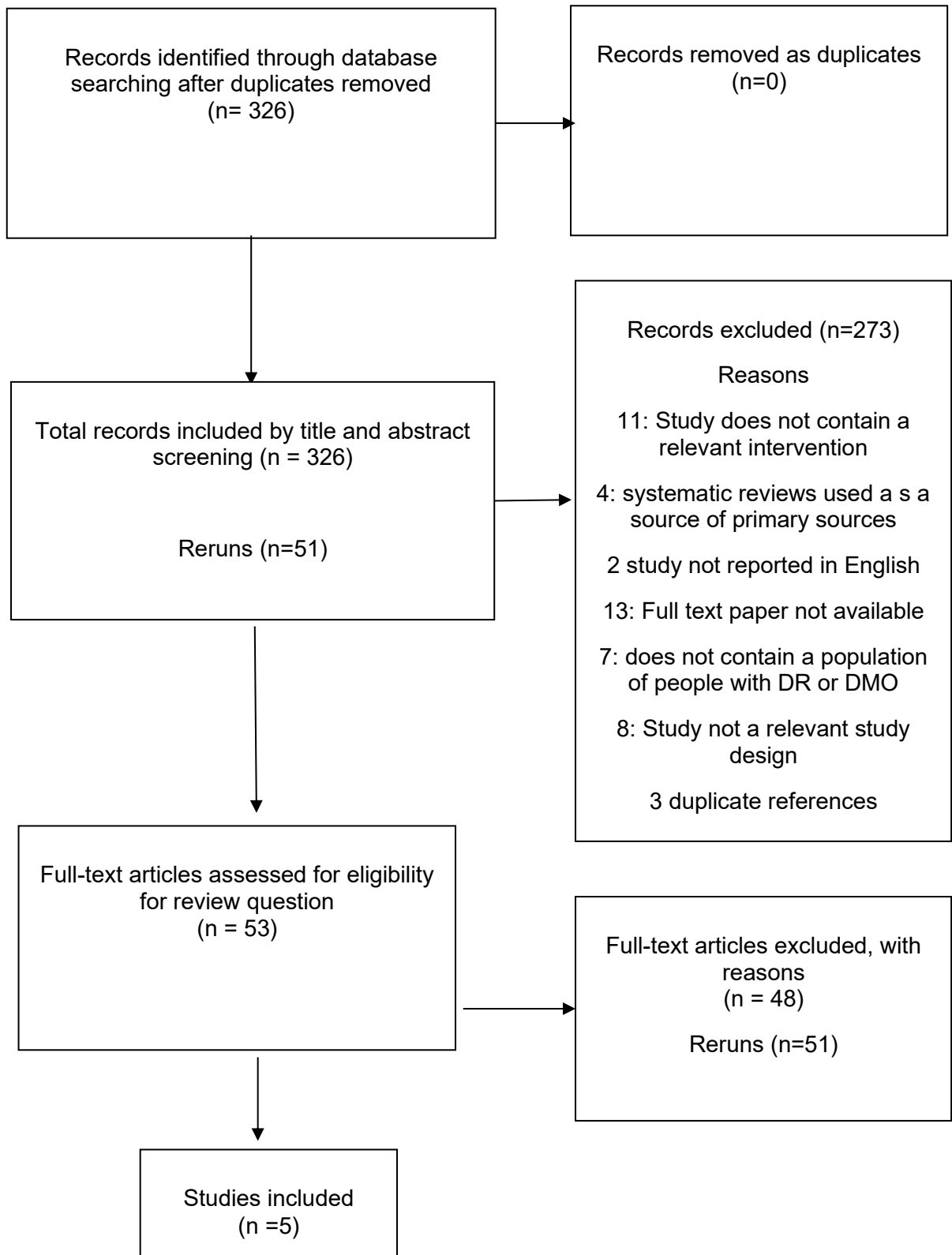
## **Appendix C –Effectiveness evidence study selection**

### **C.1 Blood pressure control interventions**

This question was answered by using a recently published Cochrane review ([Do et al. 2023](#))

Details of the study selection can be found in Figure 1 (Study selection flow diagram) of the published Cochrane review. Additionally, the included papers were screened against the protocol to ensure they matched the population and interventions specified in the review protocol.

## C.2 Statins



### C.3 Fibrates

This question was answered by using a recently published Cochrane review ([Kataoka et al. 2023](#)).

Details of the study selection can be found in Figure 1 (Study selection flow diagram) of the published Cochrane review. Additionally, the included papers were screened against the protocol to ensure they matched the population and interventions specified in the NICE review protocol.

## 1 Appendix D – Effectiveness evidence

2

### D.1 Blood pressure control interventions

4 This question was answered by using a recently published Cochrane review [Do et al 2023](#)

5 Details of the study selection, evidence tables and risk of bias assessments can be found in the published Cochrane review. Additionally, the  
6 included papers were screened against protocol to match population in the reviews protocol.

7

8 **Do, 2023**

**Bibliographic Reference** Do DV; Han G; Abariga SA; Sleilati G; Vedula SS; Hawkins BS; Blood pressure control for diabetic retinopathy.; The Cochrane database of systematic reviews; 2023; vol. 3 (no. 3)

9 **Study Characteristics**

<b>Study design</b>	Systematic review
<b>Study details</b>	<p>Dates searched.</p> <p>Last searched on 3 September 2021</p> <p>Databases searched.</p> <ul style="list-style-type: none"> <li>• Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 9) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 3 September 2021)</li> <li>• MEDLINE Ovid (1946 to 3 September 2021)</li> <li>• Embase.com (1947 to 3 September 2021)</li> </ul>

	<ul style="list-style-type: none"> <li>• Latin American and Caribbean Health Sciences Literature database (LILACS) (1982 to 3 September 2021)</li> <li>• US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (<a href="http://www.clinicaltrials.gov/">www.clinicaltrials.gov/</a>; searched 3 September 2021)</li> <li>• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<a href="http://www.who.int/clinical-trials-registryplatform">www.who.int/clinical-trials-registryplatform</a>; searched 3 September 2021)</li> </ul> <p>Sources of funding</p> <p>Eight trials were sponsored entirely by pharmaceutical companies (ABCD-2V (1); BENEDICT; DEMAND; DIRECT Prevent 1; DIRECT Protect 1; DIRECT Protect 2; EUCLID; ROADMAP). Ten trials were conducted with partial support from industry and additional support from governmental agencies and foundations (ABCD (1); ABCD (2); ACCORD Eye; BENEDICT; Chase; Knudsen; Medi-Cal; RASS; Steno-2; UKPDS/HDS). Partial support from industry was typically in the form of study drugs and supplies or support for conducting specific procedures or analyses. Nine trials were conducted with support exclusively from governmental agencies, foundations, or grants from participating institutions (AddIT; ADDITION-Europe; ADVANCE/AdRem; HINTS; J-EDIT; Pradhan; Ravid 1993; Wang; Zhao). Source of funding to conduct the trial was not reported in Larsen or Rachmani 2002.</p>
<b>Inclusion criteria</b>	<p>Type of studies</p> <p>Randomised controlled trials</p> <p>Type of participants</p> <p>Participants with a diagnosis of either type 1 or type 2 diabetes, irrespective of age, gender, ethnicity, ancestry, status regarding blood pressure or its treatment, or diabetic retinopathy status.</p> <p>Type of interventions</p> <p>Trials in which:</p> <ul style="list-style-type: none"> <li>• participants assigned to more intense blood pressure control, alone or in combination with other interventions, were compared with participants assigned to less intense blood pressure control;</li> <li>• participants assigned to blood pressure control were compared with participants assigned to usual care or no intervention on blood pressure (placebo);</li> </ul>

	<ul style="list-style-type: none"> <li>• participants assigned to antihypertensive agents versus placebo;</li> <li>• participants assigned to treatment with one class of antihypertensive agent were compared with participants assigned to another class of antihypertensive agent.</li> </ul>
<b>Exclusion criteria</b>	No exclusion criteria were listed in the section of methods
<b>Intervention(s)</b>	Antihypertensive medication  Placebo
<b>Outcome(s)</b>	Visual acuity  Incidence of proliferative diabetic retinopathy  Incidence of diabetic macular oedema  Vision related quality of life
<b>Number of studies included in the systematic review</b>	29 RCTs
<b>Studies from the systematic review that are relevant for use in the current review</b>	ACCORD  ADVANCE/AdRem  DIRECT Protect 1  DIRECT Protect 2  JEDIT  UKPDS/HDS
<b>Studies from the systematic review</b>	<ul style="list-style-type: none"> <li>• These studies were excluded because they included people who had diabetes with no retinopathy at baseline.</li> <li>• ABCD (1)</li> </ul>

<p><b>that are not relevant for use in the current review</b></p>	<ul style="list-style-type: none"> <li>• ABCD (2)</li> <li>• ABCD-2V (1)</li> <li>• AdDIT</li> <li>• ADDITION-Europe</li> <li>• BENEDICT</li> <li>• Chase</li> <li>• DEMAND</li> <li>• DIRECT Prevent 1</li> <li>• EUCLID</li> <li>• HINTS</li> <li>• J-DOIT3</li> <li>• Knudsen</li> <li>• Larsen</li> <li>• Medi-Cal</li> <li>• Pradhan</li> <li>• Rachmani 2002</li> <li>• RASS</li> <li>• Ravid 1993</li> <li>• ROADMAP</li> <li>• Steno-2</li> <li>• Wang</li> <li>• Zhao</li> </ul>
<p><b>Additional comments</b></p>	<p>the NICE team have screened the studies included in the Cochrane review against the review protocol in Appendix A. The list of studies that met the inclusion criteria for the current review are listed. The applicability and risk of bias assessment were conducted in the Cochrane review were used in this review.</p>

10

11

12 **Critical appraisal - ROBIS checklist**

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable <i>(ACCORD included population with proliferative retinopathy at baseline)</i>

13

## 1D.2Statins

### 15 Chew, 2014 (ACCORD)

**Bibliographic Reference** Chew, Emily Y; Davis, Matthew D; Danis, Ronald P; Lovato, James F; Perdue, Letitia H; Greven, Craig; Genuth, Saul; Goff, David C; Leiter, Lawrence A; Ismail-Beigi, Faramarz; Ambrosius, Walter T; Action to Control Cardiovascular Risk in Diabetes Eye Study Research, Group; 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; vol. 121 (no. 12); 2443-51

### 16 Study details

<b>Trial registration number and/or trial name</b>	NCT00542178 for the ACCORD Eye study.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	USA and Canada
<b>Study setting</b>	<b>Not reported</b>
<b>Study dates</b>	Recruitment in the ACCORD trial began with a vanguard phase in January 2001; the main trial began in February 2003. The ACCORD Eye study began in October 2003, with 3537 participants enrolled by February 2006.



<b>Sources of funding</b>	National Heart, Lung, and Blood Institute, National Institutes of Health (NHI), National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the national Institute on Aging, Center for Disease Control and Prevention Tablets of fenofibrate, equipment's and supplies were provided by a pool of pharmaceuticals companies
<b>Inclusion criteria</b>	people with an HDL cholesterol level of less than 55 mg per decilitre; (1.4 mmol per liter) for women and for black ethnicity, and less than 50 mg per deciliter (1.3 mmol per liter) for all other people.
<b>Exclusion criteria</b>	People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded.
<b>Intervention(s)</b>	Group 1: fenofibrate 160 mg/day plus simvastatin (n =806)
<b>Comparator</b>	Group 2: placebo plus simvastatin (n =787)
<b>Number of participants</b>	1593
<b>Duration of follow-up</b>	4 years
<b>Loss to follow-up</b>	(82.3%) participants had both baseline and year 4 follow-up data available for analyses
<b>Methods of analysis</b>	
<b>Additional comments</b>	Type 2 diabetes, moderate dyslipidaemia, established cardiovascular disease or cardiovascular risk factors (n =1594)  Age (yr) 61.6 (6.3) Female:501 Diabetes Duration (yr) 10.0 (7.1)

<b>Baseline characteristics</b>	
---------------------------------	--

17 **Study arms**18 **simvastatin plus fenofibrate (N = 806)** 160 mg daily of fenofibrate plus simvastatin19 **simvastatin plus Placebo (N = 787)** placebo plus simvastatin20 **Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Overall bias and Directness	Risk of bias judgement	Moderate (Data was not available for all/nearly all participants randomised - 85% of people returned for the second eye examination)
Overall bias and Directness	Overall Directness	Partially applicable some people had PDR rather than NPDR

21

22 **Gupta, 2004****Bibliographic Reference**

Gupta, Amod; Gupta, Vishali; Thapar, Shveta; Bhansali, Anil; Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema.; American journal of ophthalmology; 2004; vol. 137 (no. 4); 675-82

23 **Study details**

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	India
<b>Study setting</b>	Retina Clinic of tertiary-care referral institute.
<b>Study dates</b>	Not reported

<b>Sources of funding</b>	not detailed
<b>Inclusion criteria</b>	<p>People with noninsulin dependent diabetes mellitus with non-proliferative diabetic retinopathy and macular oedema characterized by the presence of retinal thickening within one disc diameter of the centre of macula that was associated with hard exudates of grade 4 or more in field.</p> <p>(1) diabetes mellitus of at least 5 years' duration.</p> <p>(2) abnormal baseline lipid profile (serum cholesterol 200 mg/dl, low-density lipoprotein [LDL] 100 mg/dl, or serum triglycerides 200 mg/dl); or</p> <p>(3) non proliferative diabetic retinopathy with clinically significant macular oedema having hard exudates of at least grade 4 in field</p>
<b>Exclusion criteria</b>	people with macular ischemia, pseudophakia, poorly controlled hypertension, associated vascular occlusions, media opacities, debilitating systemic diseases, coronary artery diseases, and any hepatic or muscular diseases were excluded from the study, as were pregnant patients.
<b>Intervention(s)</b>	<p>After randomization and during the metabolic control period, 15 patients enrolled in group A received oral atorvastatin 10 mg/d; later, the dose was further regulated, depending on the lipid profile, with an attempt to achieve a total cholesterol concentration of 150 mg/dl, after which the patients continued to receive maintenance therapy. Liver function tests were performed for all these patients before initiating atorvastatin therapy.</p> <p>After achieving the target metabolic control in both groups and desirable lipid profiles in group A, focal/grid laser photocoagulation of macula was done for all the eyes in both groups with a frequency-doubled Nd:YAG green laser (532 nm)</p>
<b>Comparator</b>	<p>In group B, 15 patients were subjected to metabolic control but did not receive any lipid-lowering therapy</p> <p>After achieving the target metabolic control in both groups and desirable lipid profiles in group A, focal/grid laser photocoagulation of macula was done for all the eyes in both groups with a frequency-doubled Nd: YAG green laser (532 nm)</p>
<b>Outcome measures</b>	Visual acuity

	Progression of DR (macular oedema, distribution of hard exudates)
<b>Number of participants</b>	Non-proliferative diabetic retinopathy with clinically significant macular oedema (n =30)
<b>Duration of follow-up</b>	18 weeks
<b>Loss to follow-up</b>	0 lost to follow up
<b>Baseline characteristics</b>	Age (yr.): <b>atorvastatin</b> :55.53 (8.29) <b>placebo</b> 52.73 (7.27) Sex, M:F <b>atorvastatin</b> 10:5 <b>placebo</b> 11:4

24

25 **Study arms**26 **atorvastatin (N = 15)** Group 1: atorvastatin 10 mg/day both groups received also Nd Yag Green laser (532 Nm)27 **placebo (N = 15)** Group 2: no intervention (n=15) Both groups received also Nd Yag Green laser (532 Nm)28 **Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

29

30 **Murakami, 2021**

**Bibliographic Reference** Murakami, Tomoaki; Kato, Satoshi; Shigeeda, Takashi; Itoh, Hiroshi; Komuro, Issei; Takeuchi, Masahiro; Yoshimura, Nagahisa; ophthalmology substudy of EMPATHY, Investigators; Intensive treat-to-target statin therapy and severity of diabetic retinopathy complicated by hypercholesterolaemia.; Eye (London, England); 2021; vol. 35 (no. 8); 2221-2228

31

32 **Study details**

<b>Secondary publication of another included study- see primary study for details</b>	a prespecified ophthalmology sub study of the EMPATHY study, which used a multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) design
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Japan
<b>Study setting</b>	ophthalmology departments at prevention sites (hospitals and clinics)
<b>Study dates</b>	between May 2010 and October 2013.
<b>Sources of funding</b>	supported by Shionogi & Co., Ltd.
<b>Inclusion criteria</b>	Patients in the EMPATHY study (Age at least 30 years, Man; or woman who not of child-bearing potential during the study, Outpatient, Hypercholesterolemia with LDL-C $\geq$ 120 mg/dL for previously untreated patients or $\geq$ 100 mg/dL for those treated with a single statin or other lipid-lowering drug, Type 2 diabetes, No history of CAD (myocardial infarction, angina, or coronary revascularization) who had seven-field fundus photographs taken at enrolment and after three years (36 &#177; 3 months) were eligible for participation in sub study
<b>Exclusion criteria</b>	People with a history of hypersensitivity to statins, History of drug-associated muscle disorder, History of CAD (myocardial infarction, angina, or coronary revascularization), History of stroke (including revascularization), Symptomatic PAD, Uncontrolled hypertension with DBP $\geq$ 120 mmHg or SBP $\geq$ 200 mmHg, or hypertensive emergency vii) New York Heart Association class M or higher, Valvular heart disease with serious hemodynamic abnormality, Hypercholesterolemia treated with two or more lipid-lowering drugs, Familial hypercholesterolemia, Serious coexisting illness such as malignant tumor, or severely limited life expectancy (patients are eligible if they received no treatment for at least 5 years and have experiences no relapse of malignancy), Renal failure necessitating transplantation or dialysis, Patient is pregnant, could be pregnant, or wishes to become pregnant during the study

<b>Intervention(s)</b>	Patients were randomly assigned to oral intensive statin therapy (targeting LDL-C below 70 mg/dL)
<b>Comparator</b>	standard statin therapy (targeting LDL-C between 100 and 120 mg/dL),
<b>Outcome measures</b>	Incidence of DR (ETDRS) Visual acuity (Logarithm of the Minimum Angle of Resolution, LogMAR)
<b>Number of participants</b>	219
<b>Duration of follow-up</b>	36 ± 3 months

33 **Study arms**

34 **Intensive statin therapy (N = 85)** Oral intensive statin therapy (targeting LDL-C below 70 mg/dL)

35 **standard statin therapy (N = 72)** standard statin therapy (targeting LDL-C between 100 and 120 mg/dL)

36 **Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Overall bias and Directness	Risk of bias judgement	Moderate - high attrition
Overall bias and Directness	Overall Directness	Directly applicable

37

38 **Narang, 2012**

**Bibliographic Reference** Narang, S; Sood, S; Kaur, B; Singh, R; Mallik, A; Kaur, J; Atorvastatin in clinically-significant macular oedema in diabetics with a normal lipid profile.; Nepalese journal of ophthalmology: a biannual peer-reviewed academic journal of the Nepal Ophthalmic Society : NEPJOPH; 2012; vol. 4 (no. 1); 23-8

39 **Study details**

Diabetic Retinopathy: management and monitoring evidence reviews for different monitoring frequencies DRAFT FOR CONSULTATION (August 2023)

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	India
<b>Study setting</b>	Retina services of our institute which is a tertiary eye care centre.
<b>Sources of funding</b>	not detailed
<b>Inclusion criteria</b>	People with non-proliferative diabetic retinopathy (NPDR) with CSME diabetic patients with normal lipid profile i.e. total cholesterol < 190mg %, LDL < 115mg %, HDL > 40mg % and serum triglycerides < 180mg In case of bilateral CSME, worse eye was included in the study.
<b>Exclusion criteria</b>	People with significant media opacities that precluded fundus photography / fundus fluorescein angiography, any other ocular ailment or ocular or systemic surgery within three months before randomization, diabetic retinopathy with macular ischemia, cystoid macular oedema, proliferative diabetic retinopathy, neovascularization of iris, very severe non proliferative diabetic retinopathy, cases of myopathy, hepatic disease, myocardial infarction or other heart ailments, uncontrolled hypertension, nephropathy (serum creatinine > 2 mg %), anaemia with haemoglobin less than 10gm %, debilitating systemic illness and uncontrolled blood sugar level., pregnant females, premenopausal females, patients with acute liver or renal disease, idiopathic lung fibrosis or patients who were already on statins or immunosuppressants.
<b>Intervention(s)</b>	Group A patients were administered Atorvastatin (daily dose of 20 mg) throughout the study period starting four weeks prior to laser treatment.
<b>Comparator</b>	Group B patients were given placebo during study period.
<b>Outcome measures</b>	Visual acuity Progression of DR (distribution of hard exudates)
<b>Number of participants</b>	30

<b>Duration of follow-up</b>	All patients had minimum of six months follow up. The follow up was scheduled at three monthly intervals
<b>Loss to follow-up</b>	0
<b>Methods of analysis</b>	Both the groups were compared using unpaired t test for quantitative parameters and chi square test for qualitative parameters.
<b>Baseline characteristics</b>	The duration of diabetes ranged from five to 25 years (mean of 11.93 + 3.83 in group A and 10.53 + 5.62 in group B).  The study included 30 patients with age ranging from 40 -75 years with the mean of 58.2 ±6.85 in group A and 53.6 ± 7.65 in group B. Male to female ratio was similar in both the groups. All were metabolically stable NIDDM patients at the time of randomization

40 **Study arms**

41 **Atorvastatin (N = 15)** Group A patients were administered Atorvastatin (daily dose of 20 mg) throughout the study period starting four weeks prior  
42 to laser treatment.

43 **Placebo (N = 15)** Group B patients were given placebo during study period

44 **Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

45 **Sen, 2002**

**Bibliographic Reference** Sen, Kaushik; Misra, Anoop; Kumar, Atul; Pandey, Ravindra Mohan; Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia.; Diabetes research and clinical practice; 2002; vol. 56 (no. 1); 1-11

46 **Study details**

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<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	India
<b>Sources of funding</b>	Provision of tablets of simvastatin and placebo from Ranbaxy Laboratories
<b>Inclusion criteria</b>	<p>People with non-proliferative diabetic retinopathy with no clinically significant macular oedema</p> <p>Patients with diabetes mellitus (Type 1 and 2) with DR attending the ophthalmology and medicine out-patients departments were eligible for the study.</p> <p>Ophthalmologic inclusion criteria were:</p> <ol style="list-style-type: none"> <li>1. non-clinically significant macular oedema either in one or in both eyes (hard exudates or retinal thickening at least 500 away from fovea. Hard exudates and macular oedema had to be either 'definite' or 'questionable' as per ETDRS grading).</li> <li>2. VA 6/24 or better in one or both eyes.</li> <li>3. Leaking capillaries, intra-retinal microvascular abnormalities (IRMAs), and/or microaneurysms at least 500 away from fovea in one or both eyes.</li> <li>4. No laser photocoagulation in last year.</li> <li>5. Absence of clinically significant macular oedema (CSME), proliferative DR, age-related macular degeneration, any other macular pathology (excluding diabetic macular oedema), any media opacity (cataract, corneal opacity and vitreous haemorrhage), or glaucoma.</li> </ol>
<b>Exclusion criteria</b>	People showing either mild background DR or proliferative DR or CSME was excluded
<b>Intervention(s)</b>	simvastatin 20-mg per day
<b>Comparator</b>	placebo
<b>Outcome measures</b>	Incidence of DR (macular oedema)

	Visual acuity
<b>Number of participants</b>	50
<b>Duration of follow-up</b>	3 months
<b>Loss to follow-up</b>	A total of 133 patients were evaluated, and 50 recruited for the study all 50 were analysed
<b>Baseline characteristics</b>	Mean (S.D.) age were 54.9 (7.8) and 53.0 (10.2) years in the simvastatin and placebo groups

47 **Study arms**

48 **simvastatin 20 mg/day (N = 25)**

49 **placebo (N = 25)**

50 **Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Overall bias and Directness	Risk of bias judgement	Moderate (not all outcomes. in protocol reported)
Overall bias and Directness	Overall Directness	Directly applicable

**5D.3 Fibrate**

52 This part of the review question was answered by using a recently published Cochrane review [Kataoka et al 2023](#).

53 Details of the study selection, evidence tables and risk of bias assessments can be found in the published Cochrane review. Additionally, the  
 54 NICE team have screened the studies included in the Cochrane review against the review protocol in [Appendix A](#). The list of studies that met the  
 55 inclusion criteria for the current review are listed in the table below.

56

57 **Kataoka, 2023**

**Bibliographic Reference** Kataoka SY, Lois N, Kawano S, Kataoka Y, Inoue K, Watanabe N. Fenofibrate for diabetic retinopathy. Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD013318

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59 **Study Characteristics**

<b>Study design</b>	Systematic review
<b>Study details</b>	<p>Dates searched.</p> <p>The date of the search was 1 February 2022.</p> <p>Databases searched.</p> <ul style="list-style-type: none"> <li>• Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 2) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 1 February 2022)</li> <li>• MEDLINE Ovid (1946 searched 1 February 2022)</li> <li>• Embase Ovid (1980 searched 1 February 2022)</li> <li>• ISRCTN registry (<a href="http://www.isrctn.com/editAdvancedSearch">www.isrctn.com/editAdvancedSearch</a>; searched 1 February 2022)</li> <li>• US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>; searched 1 February 2022)</li> <li>• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<a href="http://www.who.int/ictrp">www.who.int/ictrp</a>; searched 1 February 2022)</li> </ul> <p>Sources of funding</p> <p>ACCORD: their study was supported from the National Heart, Lung, and Blood Institute, the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute on Aging, and the Centers for Disease Control and Prevention. General Clinical Research Centers provided support at many sites. The following companies donated study medications, equipment, or supplies: Abbott Laboratories, Amylin</p>

	<p>Pharmaceutical, AstraZeneca Pharmaceuticals, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline Pharmaceuticals, King Pharmaceuticals, Merck, Novartis Pharmaceuticals, Novo Nordisk, Omron Healthcare, Sanofi-Aventis U.S., and Takeda Pharmaceuticals.</p> <p>FIELD: this study was supported by a grant from Laboratoires Fournier SA, Dijon, France, and by the National Health and Medical Research Council of Australia.</p>
<b>Inclusion criteria</b>	<p>Type of studies</p> <p>Randomised controlled trials</p> <p>Type of participants</p> <p>Participants were people diagnosed with type 1 or type 2 diabetes. People who did not have retinopathy or who had non-proliferative diabetic retinopathy at baseline. Studies randomising participants with and without complications of diabetic retinopathy (i.e. diabetic macular oedema/proliferative diabetic retinopathy) were included if the proportion of people with complications was low (i.e. less than 10%) or if data on people without complications were presented separately.</p> <p>Type of interventions</p> <p>Intervention: fenofibrate (any dose/regimen)</p> <p>Comparison: placebo or observation</p>
<b>Exclusion criteria</b>	<p>Type of studies</p> <p>Post-trial follow-up studies</p> <p>Type of participants</p> <p>Studies including only participants with established complications of diabetic retinopathy (i.e. diabetic macular oedema/proliferative diabetic retinopathy) were excluded.</p>
<b>Intervention(s)</b>	Placebo

	Fenofibrate
<b>Outcome(s)</b>	Visual acuity Incidence of proliferative diabetic retinopathy Incidence of diabetic macular oedema Vision related quality of life
<b>Number of studies included in the systematic review</b>	2 RCTs
<b>Studies from the systematic review that are relevant for use in the current review</b>	ACCORD FIELD
<b>Studies from the systematic review that are not relevant for use in the current review</b>	None - all are relevant and included in the NICE review

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### Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low

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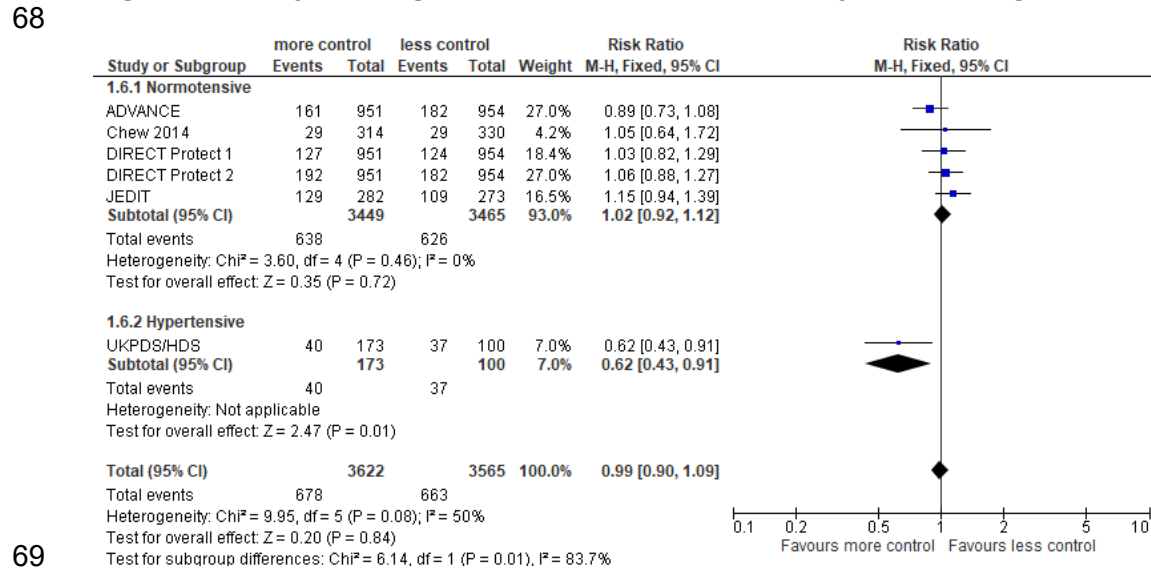
Section	Question	Answer
Overall study ratings	Applicability as a source of data	Partially applicable <i>(Subgroup with diabetic retinopathy included a large proportion (&gt;50%) with mild non-proliferative retinopathy. FIELD study included population with proliferative retinopathy at baseline.)</i>

63 **Appendix E – Forest Plots**

64 **E.1 Blood pressure control interventions**

65 **More blood pressure control versus less blood pressure control**

67 **Figure 1: Five-year progression of diabetic retinopathy - worsening of 2 steps or more on the ETDRS retinopathy severity scale**



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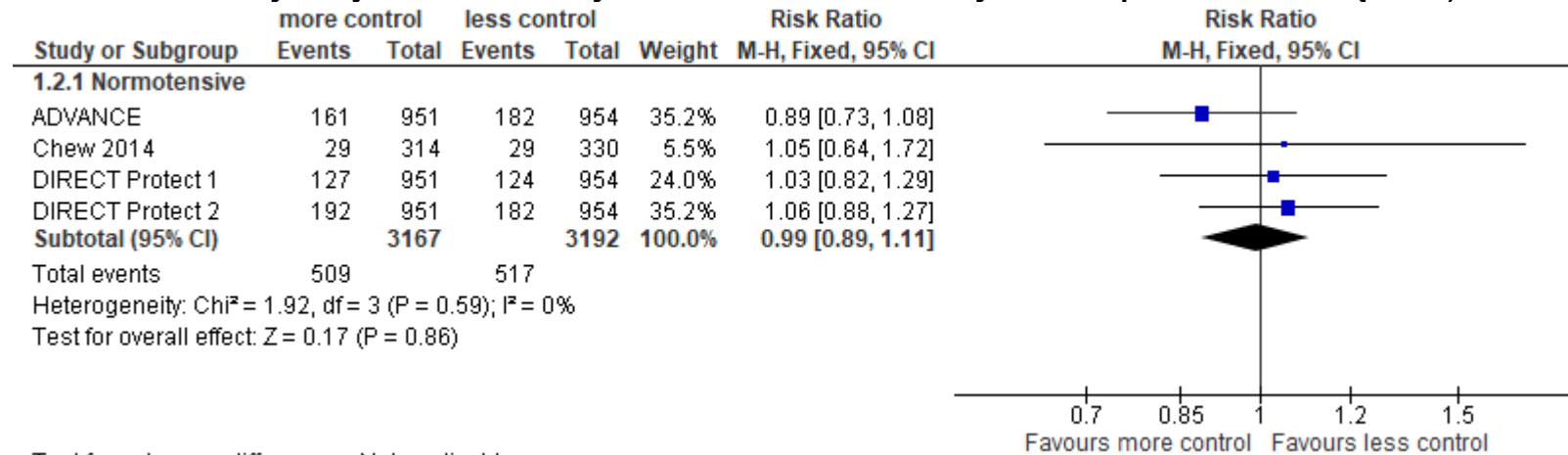
75 **Sensitivity analysis**

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**Figure 2: Five-year progression of diabetic retinopathy - worsening of 2 steps or more on the ETDRS retinopathy severity scale. Sensitivity analysis with the study that does not relate directly to blood pressure control {JEDIT} removed.**



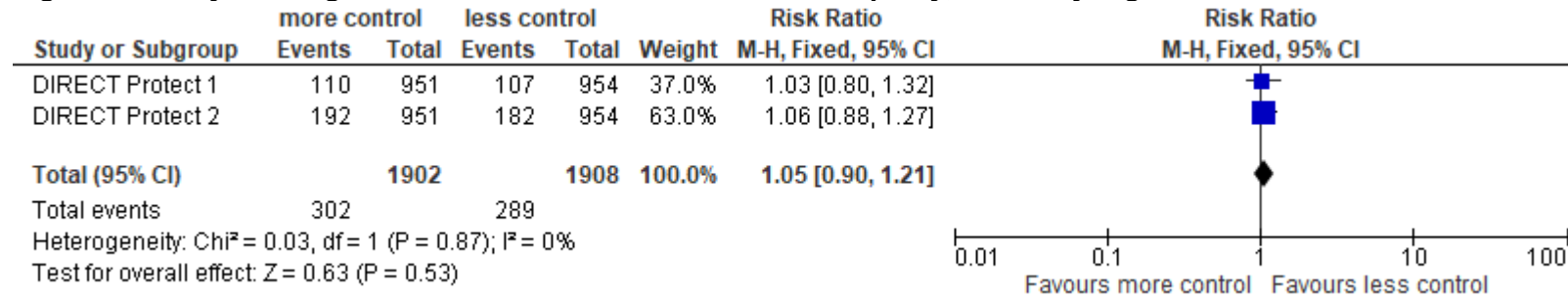
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Test for subgroup differences: Not applicable

**Figure 3: Five-year Progression to Proliferative Diabetic Retinopathy, Clinically Significant Macular oedema, or vitreous haemorrhage**

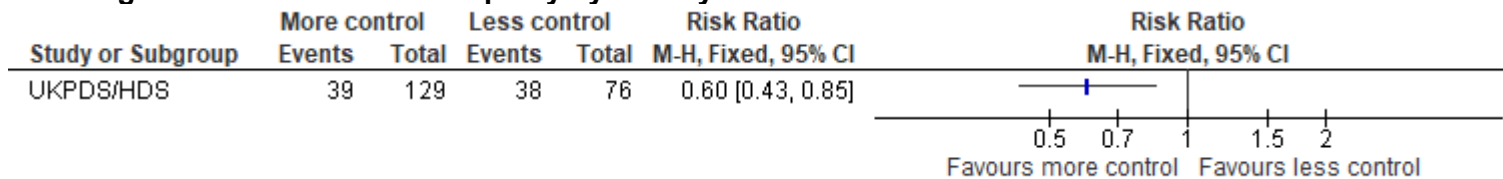


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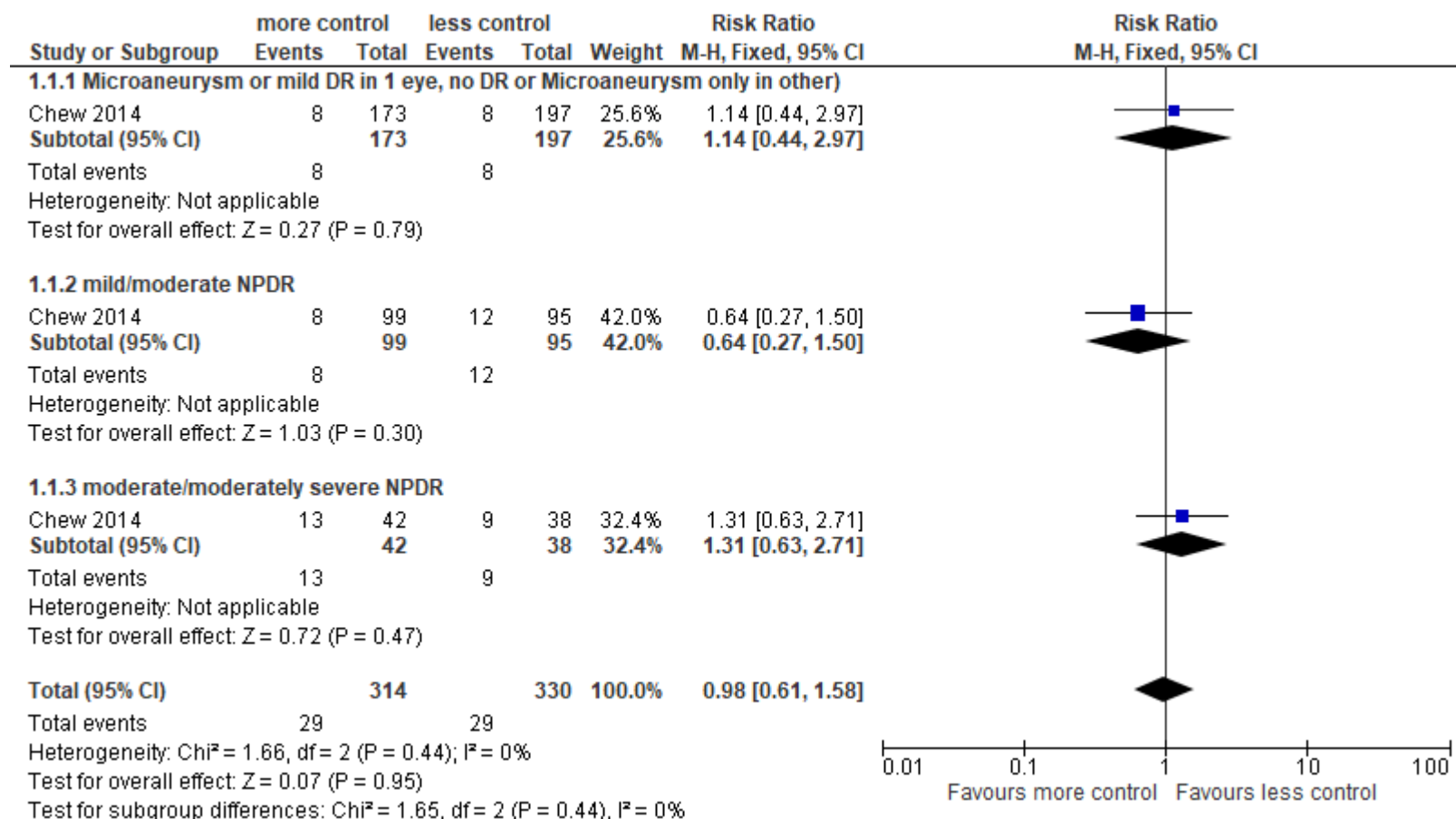
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**Figure 4: Progression of diabetic retinopathy by 7 to 9 years**



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87 **Figure 5: Four-Year Rates of Diabetic Retinopathy Severity Progression**



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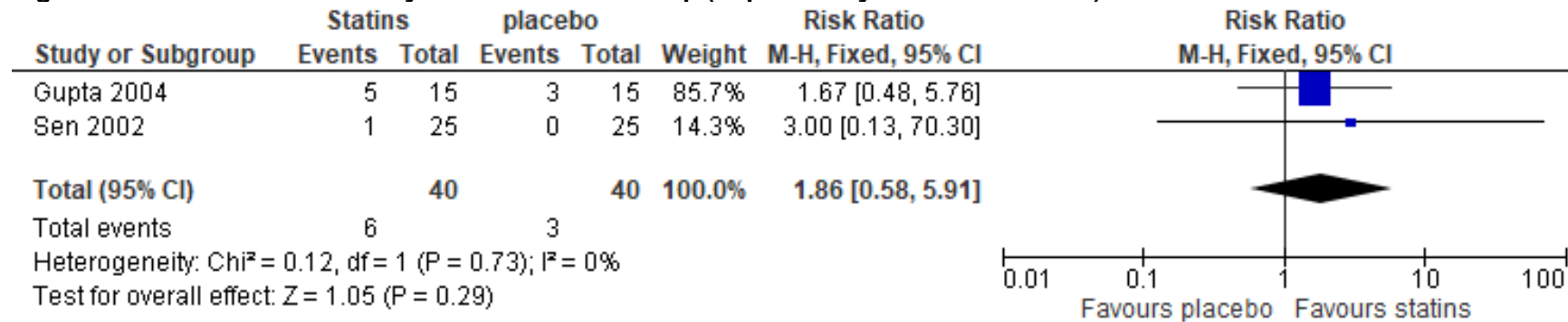
## 9E.2 Statins

93 **Statins vs Placebo**

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**Figure 6: Status of Visual Acuity at 18-Week Follow-up (Improved by at least two lines)**



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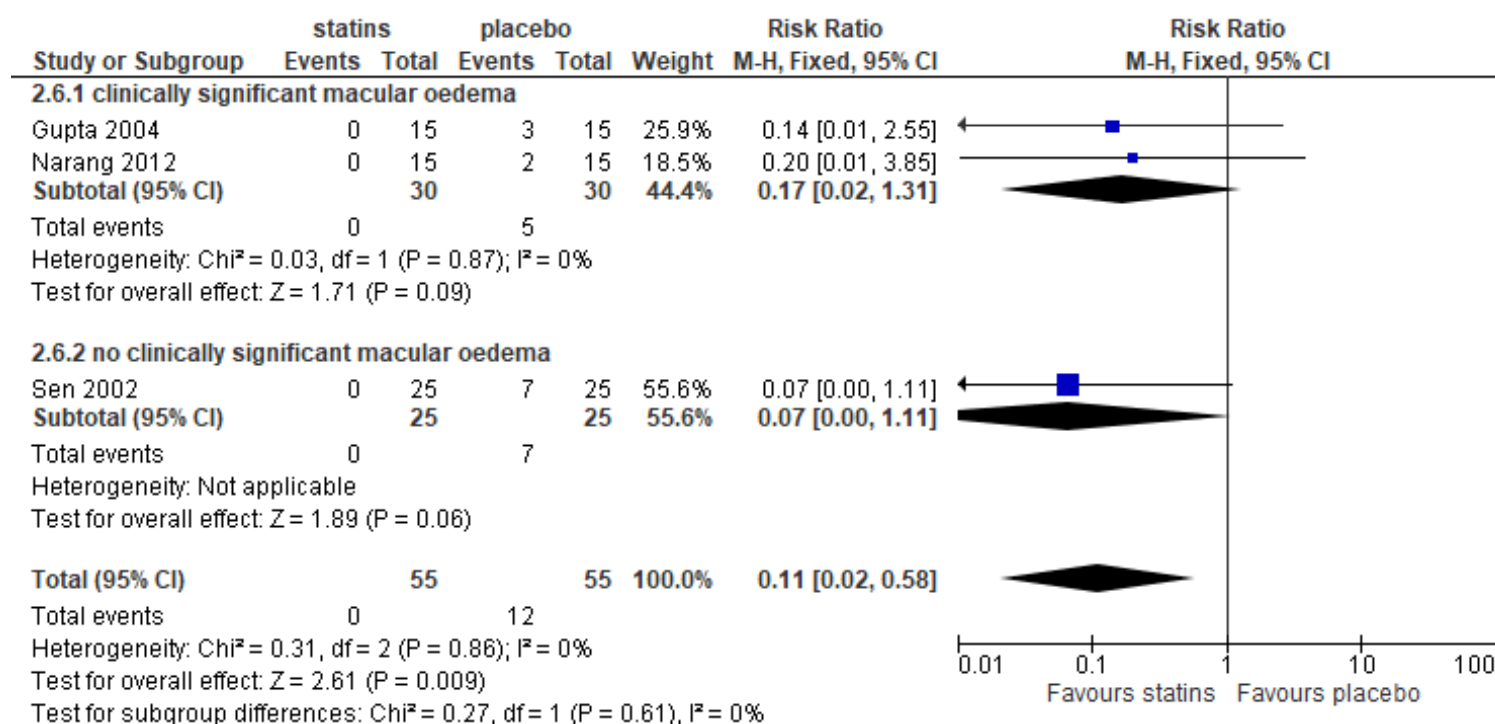
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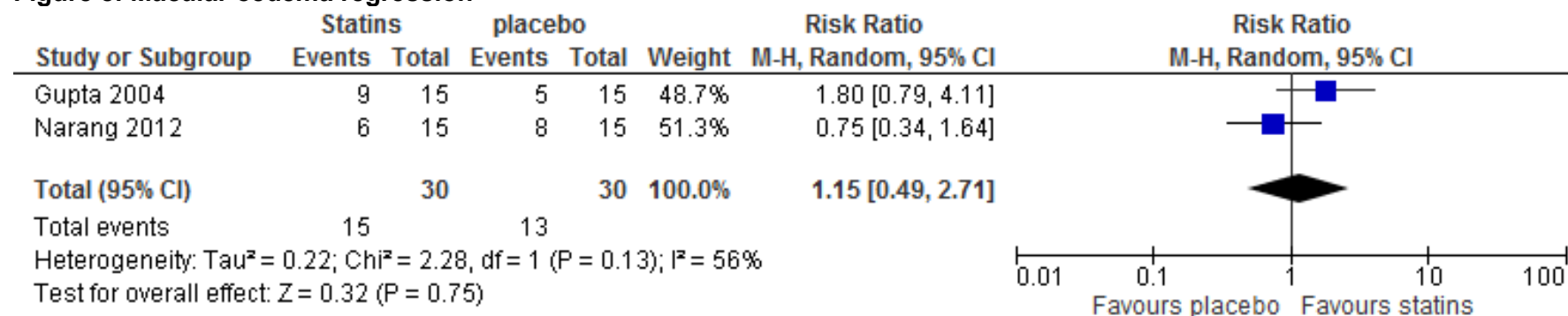
**Figure 7: Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines)**

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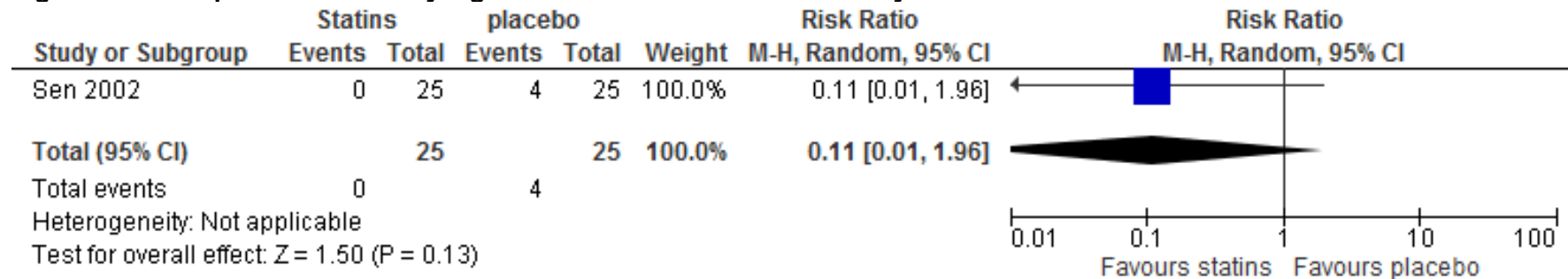
**Figure 8: Macular oedema regression**



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**Figure 9: Development of clinically significant macular oedema at 90 days**

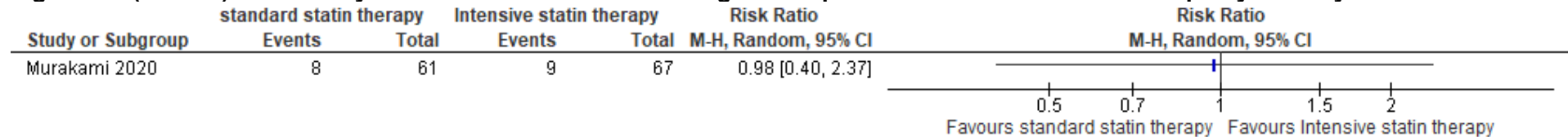


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**Intensive statin therapy vs standard statin therapy**

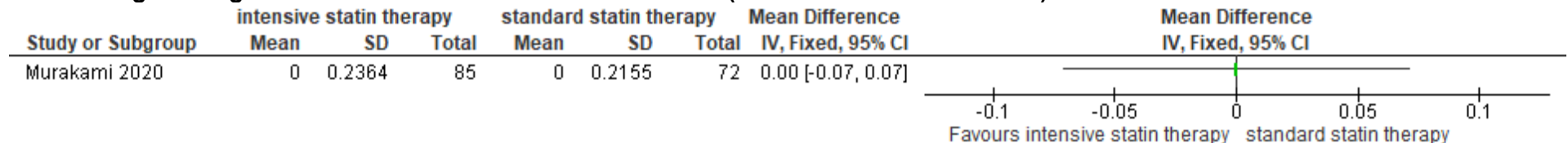
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**Figure 10: (ETDRS) DR severity scale at 36 months - worsening of 2 steps or more on the ETDRS retinopathy severity scale**



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**Figure 11: Changes in logMAR VA from baseline to last observation (Best-corrected decimal VA)**



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13 **E.3 Fibrates**

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**Fenofibrate vs placebo**

**Figure 12: 2-step progression of retinopathy progression of diabetic retinopathy.**

This was defined as at least a 2-step increase in ETDRS grade after 2 years or more of follow-up for (2-step progression of existing retinopathy in those with a baseline grade of 20 or more) and (2) primary (2-step progression to retinopathy in those with a baseline grade of 15 or less).

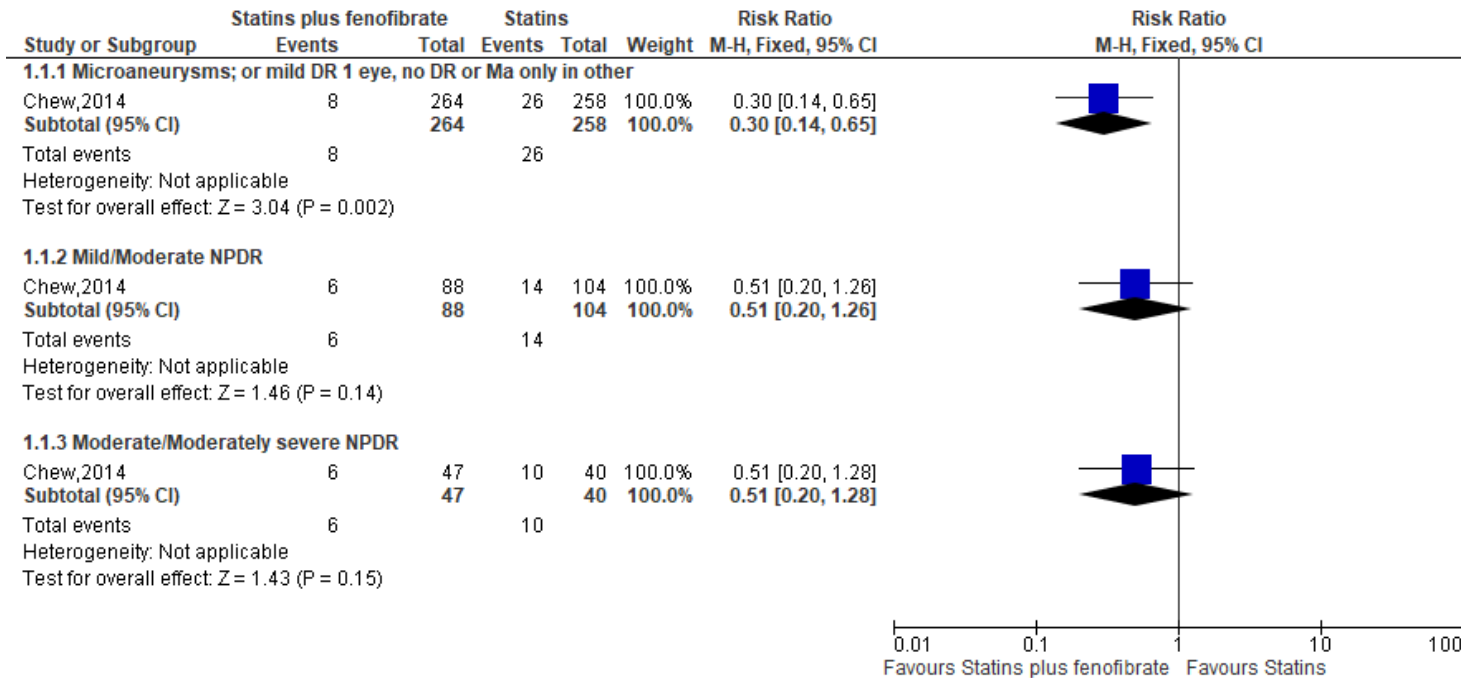


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**Statins plus fenofibrate vs Statins**

158 **Figure 13: Four-Year Rates of Diabetic Retinopathy Severity Progression.**

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162 **Appendix F GRADE tables**

163 **F.1 Blood pressure control interventions**

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165 **Table 17: Five-year progression of diabetic retinopathy - worsening of 2 steps or more on the ETDRS retinopathy severity scale**

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No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with less control	Risk with More control					
Five-year progression of diabetic retinopathy (RR<1 favours more blood pressure control)									
Normotensive at baseline									
5	RCT	6914	18 per 100	18 per 100 14 lower 22 higher	Risk Ratio: 1.02 [0.92, 1.12]	serious <sup>1</sup>	Not serious	Not serious	Moderate
Sensitivity analysis (with the study that does not relate directly to blood pressure control (JEDIT) removed).									
Hypertensive at baseline									
Normotensive at baseline									
4	RCT	6359	16 per 100	18 per 100 18 lower 18 higher	Risk Ratio: 0.99[0.89, 1.11]	serious <sup>1</sup>	Not serious	Not serious	Moderate
1	RCT	273	37 per 100	23 per 100 16 lower 34 higher	Risk Ratio: 0.62 [0.43, 0.91]	serious <sup>1</sup>	NA	Not serious	Moderate
1 >33% of weighted data from studies at moderate or high risk of bias									

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**Table 18: Five-year Progression to proliferative diabetic retinopathy clinically significant macular oedema, or vitreous haemorrhage**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with less control	Risk with More control					
Five-year Progression to PDR, CSME, or VH (RR<1 favours more blood pressure control)									
Normotensive at baseline									
2	RCT	3810	13 Per 100	12 Per 100 (9 to 16)	Risk Ratio 1.05 [0.90, 1.21]	Not serious	Not serious	Not serious	High

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**Table 19 : Progression of diabetic retinopathy by 7 to 9 years. Progression of retinopathy, defined as a two-step or greater progression from baseline on the ETDRS final scale based on evaluation of stereoscopic colour fundus photographs of eyes of participants who had**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Less control	Risk with More control					
7 to 9-year progression of diabetic retinopathy (RR<1 favours more blood pressure control)									
Hypertensive at baseline									
1	RCT	205	50 Per 100	30 Per 100 (22 to 43)	Risk Ratio 0.60 [0.43, 0.85]	Not serious	NA	Not serious	High

**diabetic retinopathy at baseline.**

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**Table 20: Four-Year Rates of Diabetic Retinopathy Severity Progression. Progression: Defined as 3 steps of progression along the ETDRS diabetic retinopathy severity scale**

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No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with less control	Risk with More control					
Overall (RR<1 favours more blood pressure control)									
Normotensive at baseline (pooled result)									
1	RCT	644	9 per 100	9 per 100 5 lower 14 higher	Risk Ratio 0.98 [0.61, 1.58]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
Microaneurysm or mild DR in 1 eye, no DR or Ma only in other)									
1	RCT	370	4 per 100	5 per 100 2 lower 12 higher	Risk Ratio: 1.14 [0.44, 2.97]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
mild/moderate NPDR (Normotensive at baseline)									
1	RCT	194	13 per 100	8 per 100 3 lower 19 higher	Risk Ratio:0.64 [0.27, 1.50]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
moderate/moderately severe NPDR									
1	RCT	80	24 per 100	31 per 100 15 lower 64 higher	Risk Ratio: 1.31 [0.63, 2.71]	serious <sup>1</sup>	no serious	serious <sup>2</sup>	Low

186 **F.2 Statins**

187 **Statins compared to Placebo**

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189 **Table 21: Statins compared to Placebo for diabetic retinopathy. Status of Visual Acuity at 18-Week Follow-up (Improved by at least two**  
 190 **lines)**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin	Risk with Placebo					
Status of Visual Acuity at 18-Week Follow-up (Improved by at least two lines) (RR >1 favours statins)									
2	RCT	80	14 per 100 4 lower to 44 higher	8 per 100	Risk Ratio 1.86 [0.58, 5.91]	serious <sup>1</sup>	Not serious	Not serious	Moderate
1 >33% of weighted data from studies at moderate or high risk of bias									

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192 **Table 22: Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines) by subgroups of with clinically significant**  
 193 **macula oedema and without clinically significant macular oedema. Status of Visual Acuity at 18-Week Follow-up (Worsened by at least**  
 194 **two lines) by subgroups of with clinically significant macula oedema and without clinically significant macular oedema.**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin	Risk with Placebo					
Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines) (RR<1 favours statins)									
Overall									
3	RCT	110	3 per 100 0 lower 13 higher	22 per 100	Risk Ratio: 0.1 [0.02, 0.58]	serious <sup>1</sup>	Not serious	Not serious	Moderate
Clinically significant macular oedema (RR<1 favours statins)									
2	RCT	60	2 Per 100	17 per 100	Risk Ratio: 0.17 [0.02, 1.31]	serious <sup>1</sup>	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin	Risk with Placebo					
			0 lower 22 higher						
No clinically significant macular oedema (RR<1 favours statins)									
1	RCT	50	2 per 100 0 lower 31 higher	28 per 100	Risk Ratio: 0.07 [0.00, 1.11]	serious <sup>1</sup>	NA	Not serious	Moderate
1 >33% of weighted data from studies at moderate or high risk of bias									

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**Table 23: Macular oedema regression – defined as a resolution or partial resolution of macular oedema**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin	Risk with Placebo					
Macular oedema regression (RR>1 favours statin)									
2	RCT	60	50 per 100 21 lower 117 higher	43 per 100	Risk Ratio: 1.15 [0.49, 2.71]	serious <sup>1</sup>	serious <sup>2</sup>	Not serious	Low
1 >33% of weighted data from studies at moderate or high risk of bias 2 I <sup>2</sup> >33%									

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**Table 24: Development of clinically significant macular oedema at 90 days**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin	Risk with Placebo					

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No. of studies	Study design	Sample size	Anticipated absolute effects*	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
Development of CSME at 90 days (RR<1 favours statins)								
1	RCT	50	2 per 100 0 lower 31 higher	16 per 100 Risk Ratio: 0.11 [0.01, 1.96]	serious <sup>1</sup>	NA	Not serious	Moderate
1 >33% of weighted data from studies at moderate or high risk of bias								

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**Intensive statin therapy vs standard statin therapy**

**Table 25: (ETDRS) DR severity scale- worsening of 2 steps or more on the ETDRS retinopathy severity scale**

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Intensive statin therapy	Risk with Standard statin therapy					
(ETDRS) DR severity scale at 36 months (RR<1 favours intensive statin therapy)									
1 Murakami 2020	RCT	128	13 per 10 5 lower 31 higher	13 per 100	Risk Ratio: 0.98 [0.40, 2.37]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
1 >33% of weighted data from studies at moderate or high risk of bias									
2 Mixed population with 50% population with mild non proliferative disease									

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**Table 26: Changes in logMAR VA from baseline to last observation (Best-corrected decimal VA)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
Changes in logMAR Visual Acuity from baseline to last observation (RR<1 favours intensive statin therapy)							
1 Murakami 2020	RCT	128	MD: 0.00 [-0.07, 0.07]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Moderate
1 >33% of weighted data from studies at moderate or high risk of bias							

2 Mixed population with 50% population with proliferative disease

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206 **F.3 Fibrates**

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208 **Fenofibrate compared to placebo for diabetic retinopathy.**

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210 **Table 27: 2-step progression of retinopathy progression of diabetic retinopathy:** Defined as at least a 2-step increase in ETDRS grade after  
211 2 years or more of follow-up for (2-step progression of existing retinopathy in those with a baseline grade of 20 or more) and (2) primary (2-step  
212 progression to retinopathy in those with a baseline grade of 15 or less).

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statins plus fenofibrate	Risk with Statin					
Progression of diabetic retinopathy (RR<1 favours fibrates)									
2 (FIELD study, ACCORD EYE study)	RCT	847	6 per 100 (4 Lower 9 higher)	15 per 100	Risk Ratio: 0.37(0.24 to 0.58)	serious <sup>1</sup>	No serious <sup>2</sup>	serious <sup>3</sup>	Low
1 >33% of weighted data from studies at moderate or high risk of bias due selective reporting of outcomes									
2 No serious inconsistency, I <sup>2</sup> < 33%									
3 Both studies downgraded for indirectness, Subgroup with diabetic retinopathy included a large proportion (>50%) with mild non-proliferative retinopathy who are outside of the scope for this guideline.									

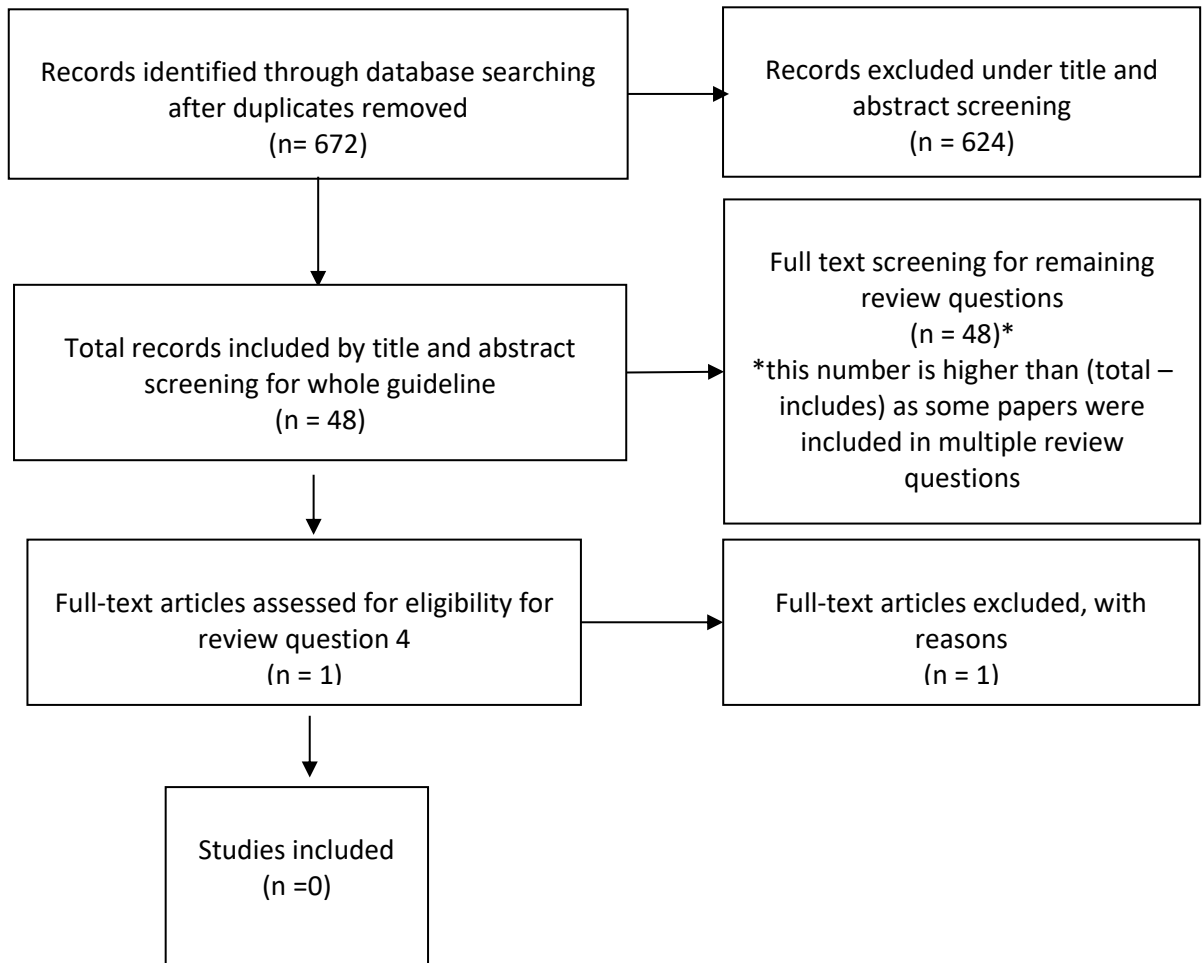
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222 **Table 28: Statins plus fenofibrate vs Statin. Four-Year Rates of Diabetic Retinopathy Severity Progression**



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No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statin plus fenofibrate	Risk with Statins only					
Microaneurysm or mild DR in 1 eye, no DR or Microaneurysm only in other) (RR<1 favours fibrates)									
1	RCT	522	3 per 100 1 lower 7 higher	10 per 100	Risk Ratio: 0.30 [0.14, 0.65]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
Mild/moderate NPDR (RR<1 favours fibrates)									
1	RCT	192	7 per 100 3 lower 18 higher	14 per 100	Risk Ratio:0.51 [0.20, 1.26]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
Moderate/moderately severe NPDR (RR<1 favours fibrates)									
1	RCT	87	13 per 100 5 lower 32 higher	25 per 100	Risk Ratio: 0.51 [0.20, 1.28]	serious <sup>1</sup>	NA	serious <sup>2</sup>	Low
1 >33% of weighted data from studies at moderate or high risk of bias									
2 Partially applicable (study included population with proliferative retinopathy at baseline)									

224 **Appendix G Economic evidence study selection**



225

226 **Appendix H – Economic evidence tables**

227 There are no included studies in this review question.

228 **Appendix I – Health economic model**

229 Original health economic modelling was not prioritised for this review question.

230 **Appendix J – Excluded studies**231 **Clinical studies**232 **Table 29: Statins studies excluded from NICE review**

Title	Reason for exclusion
Abbate, Manuela, Cravedi, Paolo, Iliev, Ilian et al. (2011) Prevention and treatment of diabetic retinopathy: evidence from clinical trials and perspectives. Current diabetes reviews 7(3): 190-200	Review article but not a systematic review
Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study, Group (2016) Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes care 39(7): 1089-100	Full text paper not available; Study does not contain a relevant intervention;
Agouridis, A.P., Rizos, C.V., Elisaf, M.S. et al. (2013) Does combination therapy with statins and fibrates prevent cardiovascular disease in diabetic patients with atherogenic mixed dyslipidemia?. Review of Diabetic Studies 10(23): 171-190	Does not contain a population of people with DR or DMO
Anonymous. (2009) Adolescent type 1 Diabetes cardio-renal Intervention Trial (AddIT). BMC Pediatrics 9: 79	Study does not contain a relevant intervention
Ansquer, Jean Claude; Crimet, Dominique; Foucher, Christelle (2011) Fibrates and statins in the treatment of diabetic retinopathy. Current pharmaceutical biotechnology 12(3): 396-405	Systematic review used as source of primary studies
Benitez-Aguirre, P., Marcovecchio, M.L., Craig, M.E. et al. (2019) Angiotensin converting enzyme inhibitor (ACEi) and statin combination therapy reduces risk of 3-step retinopathy progression in youth with type 1 diabetes (T1D) in the adolescent cardio-renal protection intervention trial (AddIT) - A post-hoc analysis based on diabetes duration. Pediatric Diabetes 20(supplement28): 10	Not a relevant study design (observational study)
Chang, C.-H. and Chuang, L.-M. (2011) Effects of medical therapies on retinopathy progression in type 2 diabetes: Is blood pressure control the lower the better?. Journal of Diabetes Investigation 2(2): 101-103	Study does not contain a relevant intervention
Chew, Emily Y, Ambrosius, Walter T, Howard, Letitia T et al. (2007) Rationale,	Duplicate reference

Title	Reason for exclusion
design, and methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE). The American journal of cardiology 99(12a): 103i-111i	
Colhoun, H M, Thomason, M J, Mackness, M I et al. (2002) Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 19(3): 201-11	Does not contain a population of people with DR or DMO
Colhoun, H.M., Betteridge, D.J., Durrington, P.N. et al. (2004) Cholesterol lowering with atorvastatin for the primary prevention of cardiovascular disease in diabetic adults. Journal of Clinical Outcomes Management 11(11): 682-685	Duplicate reference
Colhoun, HM; Betteridge, DJ; Durrington, PN (2004) Atorvastatin delays first MI for patients with diabetes. Journal of family practice 53(12): 956	Study not reported in English; Full text paper not available;
CTRI/2018/08/015308 (2018) A clinical trial to study the effect of the lipid lowering drug atorvastatin in patients with diabetes mellitus and diabetic macular edema. <a href="https://trialssearch.who.int/Trial2.aspx?TriallD=CTRI/2018/08/015308">https://trialssearch.who.int/Trial2.aspx?TriallD=CTRI/2018/08/015308</a>	Full text paper not available
CTRI/2020/07/026588 (2020) To study the effect of lipid lowering drugs in the eye manifestations of diabetic patients. <a href="https://trialssearch.who.int/Trial2.aspx?TriallD=CTRI/2020/07/026588">https://trialssearch.who.int/Trial2.aspx?TriallD=CTRI/2020/07/026588</a>	Full text paper not available
Do, D.V., Wang, X., Vedula, S.S. et al. (2015) Blood pressure control for diabetic retinopathy. Cochrane Database of Systematic Reviews 2017(6): cd006127	Systematic review used as source of primary studies
Egan, A. and Byrne, M. (2011) Effects of medical therapies on retinopathy progression in type 2 diabetes. Irish Medical Journal 104(2)	Duplicate reference
El-Azab, M.F.; Mysona, B.A.; El-Remessy, A.B. (2011) Statins for prevention of diabetic-related blindness: A new treatment option?. Expert Review of Ophthalmology 6(3): 269-272	Not a relevant study design (opinion piece)
Feher, M.D. and Elkeles, R.S. (2005) Fenofibrate in type 2 diabetes: The FIELD study. British Journal of Diabetes and Vascular Disease 5(6): 330-333	Study does not contain a relevant intervention
Gupta, V, Gupta, A, Thapar, S et al. (2002) Lipid-Lowering Drug Therapy as an Adjunct in the Management of Diabetic Macular Edema. American academy of ophthalmology: 140-141	Duplicate reference

Title	Reason for exclusion
Hamilton, S.J. and Watts, G.F. (2013) Atherogenic dyslipidemia and combination pharmacotherapy in diabetes: Recent clinical trials. Review of Diabetic Studies 10(23): 191-203	Does not contain a population of people with DR or DMO
Ikeda, S., Shinohara, K., Enzan, N. et al. (2020) Effectiveness of intensive lipid-lowering therapy with statins in type 2 diabetes mellitus patients with poorly controlled blood pressure. Hypertension 76(suppl1)	Duplicate reference
IRCT201709207466N5 (2017) The effect of treatment of hypercholesterolemia on risk of macular edema. <a href="https://trialsearch.who.int/Trial2.aspx?TriallD=IRCT201709207466N5">https://trialsearch.who.int/Trial2.aspx?TriallD=IRCT201709207466N5</a>	Full text paper not available; Study does not contain a relevant intervention;
Itoh, H.; Ueshima, K.; Komuro, I. (2018) Intensive treat-to-target statin therapy in high-risk Japanese patients with hypercholesterolemia and diabetic retinopathy: Report of a randomized study. Diabetes care 2018;41:1275-1284. Diabetes Care 41(11): e145-e146	Does not contain a population of people with DR or DMO
Itoh, Hiroshi, Komuro, Issei, Takeuchi, Masahiro et al. (2018) Intensive Treat-to-Target Statin Therapy in High-Risk Japanese Patients With Hypercholesterolemia and Diabetic Retinopathy: Report of a Randomized Study. Diabetes care 41(6): 1275-1284	Does not contain a population of people with DR or DMO
Itoh, Hiroshi, Komuro, Issei, Takeuchi, Masahiro et al. (2018) Intensive Treat-to-Target Statin Therapy in High-Risk Japanese Patients With Hypercholesterolemia and Diabetic Retinopathy: Report of a Randomized Study. Diabetes care 41(6): 1275-1284	Does not contain a population of people with DR or DMO
Jonnalagadda, V.G.; Matety, V.K.; Choudhary, K. (2018) ACE inhibitors and statins in adolescents with type 1 diabetes. New England Journal of Medicine 378(6): 579	Study does not contain a relevant intervention
JPRN-UMIN000003486 (2010) Standard versus intensive statin therapy for hypercholesterolemic patients with diabetic retinopathy. <a href="https://trialsearch.who.int/Trial2.aspx?TriallD=JPRN-UMIN000003486">https://trialsearch.who.int/Trial2.aspx?TriallD=JPRN-UMIN000003486</a>	Full text paper not available
Klein, B.E.K. (2010) Reduction in risk of progression of diabetic retinopathy. New England Journal of Medicine 363(3): 287-288	Narrative review
Lee, J., Hwang, Y.-C., Lee, W.J. et al. (2020) Comparison of the Efficacy and	Does not contain a population of people with DR or DMO

Title	Reason for exclusion
Safety of Rosuvastatin/Ezetimibe Combination Therapy and Rosuvastatin Monotherapy on Lipoprotein in Patients With Type 2 Diabetes: Multicenter Randomized Controlled Study. <i>Diabetes Therapy</i> 11(4): 859-871	
Liu, Jun, Wu, Yi-Ping, Qi, Jun-Juan et al. (2021) Effect of Statin Therapy on Diabetes Retinopathy in People With Type 2 Diabetes Mellitus: A Meta-Analysis. <i>Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis</i> 27: 10760296211040109	Does not contain a population of people with DR or DMO
Malek, M., Khamseh, M.E., Aghili, R. et al. (2012) Medical management of diabetic retinopathy: An overview. <i>Archives of Iranian Medicine</i> 15(10): 635-640	Study does not contain a relevant intervention
Matikainen, Niina; Kahri, Juhani; Taskinen, Marja-Riitta (2010) Reviewing statin therapy in diabetes--towards the best practise. <i>Primary care diabetes</i> 4(1): 9-15	Duplicate reference
Matthews, D.R. (2011) Fenofibrate and statin therapy, compared with placebo and statin, slows the development of retinopathy in type 2 diabetes patients of 10 years duration: The ACCORD study. <i>Evidence-Based Medicine</i> 16(2): 45-46	secondary publication of a ACCORD study
Misra, A; Vikram, N K; Kumar, A (2004) Diabetic maculopathy and lipid-lowering therapy. <i>Eye (London, England)</i> 18(1): 107-8	Full text paper not available
Mozetic, V., Pacheco, R.L., Latorraca, C.D.O.C. et al. (2019) Statins and/or fibrates for diabetic retinopathy: A systematic review and meta-analysis. <i>Diabetology and Metabolic Syndrome</i> 11(1): 92	Systematic review used as source of primary studies
Mozetic, Vania, Leonel, Leticia, Leite Pacheco, Rafael et al. (2019) Reporting quality and adherence of randomized controlled trials about statins and/or fibrates for diabetic retinopathy to the CONSORT checklist. <i>Trials</i> 20(1): 729	Not a relevant study design narrative review
Narang, S, Sood, S, Kaur, B et al. (2007) Role of Atorvastatin in Clinically Significant Macular Edema in Diabetics With Normal Lipid Profile. <i>American academy of ophthalmology</i> : 266	Not a relevant study design narrative review
NCT00542178 (2007) Evaluating How the Treatments in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Affect Diabetic Retinopathy (The	Full text paper not available

Title	Reason for exclusion
ACCORD Eye Study). <a href="https://clinicaltrials.gov/show/NCT00542178">https://clinicaltrials.gov/show/NCT00542178</a>	
NCT04885153 (2021) Effects of Oral Fenofibrate on Retinal Thickness and Macular Volume. <a href="https://clinicaltrials.gov/show/NCT04885153">https://clinicaltrials.gov/show/NCT04885153</a>	Full text paper not available
Nomura, A., Kawashiri, M.-A., Tada, H. et al. (2017) Serum triglyceride predicts first cardiovascular events in diabetic patients with hypercholesterolemia and retinopathy: A post-hoc analysis of a randomised controlled trial. <i>Circulation</i> 136(supplement1)	Full text paper not available
Ozkiris, A, Erkilic, K, Koc, A et al. (2007) Effect of atorvastatin on ocular blood flow velocities in patients with diabetic retinopathy. <i>The British journal of ophthalmology</i> 91(1): 69-73	Study does not contain a relevant intervention
Panagiogtoglou, TD, Ganotakis, ES, Kymionis, GD et al. (2010) Atorvastatin for diabetic macular edema in patients with diabetes mellitus and elevated serum cholesterol. <i>Ophthalmic surgery, lasers &amp; imaging</i> 41(3): 316-322	Not a relevant study design (observational study)
Saito, Yoshihiro, Nakayama, Atsuko, Sato, Tatsuyuki et al. (2020) Lipid-lowering statin therapy is beneficial in elderly female patients with hypercholesterolaemia and diabetic retinopathy. <i>European journal of preventive cardiology</i>	Study does not contain a relevant intervention
Sen, K Misra AKumar A (2000) Double Blind Randomized Trial of Efficacy of Simvastatin on Retinopathy in Hyperlipidemic Diabetic Patients. <i>Journal of the Association of Physicians of India</i>	Duplicate reference
Sharma, Neil, Ooi, Ju-Lee, Ong, Jong et al. (2015) The use of fenofibrate in the management of patients with diabetic retinopathy: an evidence-based review. <i>Australian family physician</i> 44(6): 367-70	Not a relevant study design (narrative review)
Sheth, H.G.; Aslam, S.; Davies, N. (2006) Lipid lowering drugs in diabetes: Lipid lowering has ophthalmic benefits [3]. <i>British Medical Journal</i> 332(7552): 1272-1273	Full text paper not available
Tada, H., Nomura, A., Takamura, M. et al. (2019) Fasting compared with nonfasting triglycerides and risk of cardiovascular events in diabetic patients under statin therapy. <i>Circulation</i> 140(supplement1)	Full text paper not available; Study not reported in English;
Tarantino, N., Santoro, F., De Gennaro, L. et al. (2017) Fenofibrate/simvastatin fixed-dose combination in the treatment of mixed dyslipidemia: Safety, efficacy, and place in	Study does not contain a relevant intervention

Title	Reason for exclusion
therapy. <i>Vascular Health and Risk Management</i> 13: 29-41	
Ueshima, Kenji, Itoh, Hiroshi, Kanazawa, Nobuaki et al. (2016) Rationale and Design of the Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study: a Randomized Controlled Trial. <i>Journal of atherosclerosis and thrombosis</i> 23(8): 976-90	Study does not report outcomes in protocol
Zhao, Y., Yu, X., Lou, Y. et al. (2020) Therapeutic Effect of <i>Abelmoschus manihot</i> on Type 2 Diabetic Nonproliferative Retinopathy and the Involvement of VEGF. <i>Evidence-based Complementary and Alternative Medicine</i> 2020: 5204917	Study does not contain a relevant intervention

233

234 **Table 30: Fenofibrates studies excluded by the Cochrane review**

Title	Reason for exclusion
Bonora, Bm; Albiero, M; Morieri, MI; Cappellari, R; Amendolagine, Fi; Mazzucato, M; Zambon, A; Iori, E. Avogaro, A; Fadini, Gp. Fenofibrate increases circulating haematopoietic stem cells in people with diabetic retinopathy: a randomised, placebo-controlled trial. <i>Diabetologia</i> 2021; 64:2334-2344. [DOI:10.1007/s00125-021-05532-1]	Patient population does not meet inclusion criteria
Cui, Y.; Li, X. D.. Efficacy of fenofibrate combined with 23G minimally invasive vitrectomy for diabetic retinopathy. [Chinese]. <i>International Eye Science</i> 2018;18(12):2155-2159. [DOI: <a href="http://dx.doi.org/10.3980/j.issn.1672-5123.2018.12.08">http://dx.doi.org/10.3980/j.issn.1672-5123.2018.12.08</a> ]	Patient population does not meet inclusion criteria
A Randomised Multi-Centre Placebo Controlled Trial of Fenofibrate for Treatment of Diabetic Macular Oedema with Economic Evaluation (FORTE Study). <a href="https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618000592246">https://anzctr.org.au/Trial/Registration/TrialReview.aspx?</a> ACTRN=12618000592246 April 2018. [ANZCTR: 12618000592246]	Patient population does not meet inclusion criteria
Massin, P; Peto, T; Ansquer, Jc; Aubonnet, P. Effects of fenofibric acid on diabetic macular edema: the MacuFen study. <i>Ophthalmic epidemiology</i> 2014;21(5):307-317. [DOI:10.3109/09286586.2014.949783]	Patient population does not meet inclusion criteria



Title	Reason for exclusion
Massin, P; Peto, T; Le-Malicot, K; Ansquer, J. Effects of fenofibric acid on diabetic macular edema measured by optical coherence tomography. European journal of ophthalmology. 2012;22(3):518. [DOI: 10.5301/EJO.2012.9134]	
Matthews, Dr. Fenofibrate and statin therapy, compared with placebo and statin, slows the development of retinopathy in type 2 diabetes patients of 10 years duration: the ACCORD study. Evidence-based medicine 2011;16(2):45-46. [DOI: 10.1136/ebm1155]	Patient population does not meet inclusion criteria
Srinivasan, S; Hande, P; Shetty, J; Murali, S. Efficiency of fenofibrate in facilitating the reduction of central macular thickness in diabetic macular edema. Indian journal of ophthalmology 2018;66(1):98-105. [DOI: 10.4103/ijo.IJO_566_17]	Patient population does not meet inclusion criteria

235 **Table 31: Blood pressure control studies included in the Cochrane review (Do et al.**  
236 **2023) but excluded from this review.**

Title	Reason for exclusion
ABCD (1) Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney International 2002;61(3):1086-97	People with diabetes only, no retinopathy at baseline
ABCD (2) Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23(Suppl 2):B54-64	People with diabetes only, no retinopathy at baseline
ABCD-2V (1) Estacio RO, Coll JR, Tran ZV, Schrier RW. Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. American Journal of Hypertension 2006;19:1241-8	People with diabetes only, no retinopathy at baseline
AdDIT Adolescent type 1 Diabetes cardio-renal Intervention Trial Research Group. Adolescent type 1 diabetes cardio-renal intervention trial (AdDIT). BMC Pediatrics 2009;9(1):79.	People with diabetes only, no retinopathy at baseline

Title	Reason for exclusion
<p>ADDITION-Europe</p> <p>Griffin SJ, Borch-Johnson K, Davies MJ, Khunti K, Rutten GEHM, Sandbaek A, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. <i>Lancet</i> 2011;9(378):156-67. [DOI: 10.1016/S0140-6736(11)606-98-3]</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>BENEDICT Group. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). <i>Controlled Clinical Trials</i> 2003;24(4):442-61.</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>Chase HP, Garg SK, Harris S, Hoops S, Jackson WE, Holmes DL. Angiotensin-converting enzyme inhibitor treatment for young normotensive diabetic subjects: a two-year trial. <i>Annals of Ophthalmology</i> 1993;25(8):284-9.</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>DEMAND Ruggenti P, Lauria G, Iliev IP, Fassi A, Ilieva AP, Rota S. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the Delapril and Manidipine for Nephroprotection in Diabetes (DEMAND) randomized clinical trial. <i>Hypertension</i> 2011;58(5):776-83</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>DIRECT Prevent 1 {published data only} Chaturvedi N, DIRECT Programme Study Group. The Diabetic Retinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. <i>Journal of the Renin-Angiotensin-Aldosterone System</i> 2002;3(4):255-61</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>EUCLID Chaturvedi N, Fuller JH, Pokras F, Rottiers R, Papazoglou N, Aiello LP, et al. Circulating plasma vascular endothelial growth factor and microvascular complications of type 1 diabetes mellitus: the influence of ACE inhibition. <i>Diabetes Medicine</i> 2001;18(4):288-94</p>	<p>People with diabetes only, no retinopathy at baseline</p>
<p>HINTS Bosworth H, Powers B, Olsen M, McCant F, Grubber J, Smith V, et al. Home blood pressure management and improved</p>	<p>People with diabetes only, no retinopathy at baseline</p>

Title	Reason for exclusion
bloodpressure control: results from a randomized controlled trial. Archives of Internal Medicine 2011;171(13):1173-80.	
J-DOIT3 T, Kato M, Okazaki Y, Okahata S, Katsuyama H, et al. Design of and rationale for the Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3): a multicenter, open-label, randomized, parallel-group trial. BMJ Open Diabetes Research and Care 2016;4(1):e000123. [DOI: 10.1136/bmjdr-2015-000123]	People with diabetes only, no retinopathy at baseline
Knudsen ST, Bek T, Poulsen PL, Hove MN, Rehling M, Mogensen CE. Effects of losartan on diabetic maculopathy in type 2 diabetic patients: a randomized, double-masked study. Journal of Internal Medicine 2003;254:147-58	People with diabetes only, no retinopathy at baseline
Larsen M, Hommel E, Parving HH, Lund-Andersen H. Protective effect of captopril on the blood-retina barrier in normotensive insulin-dependent diabetic patients with nephropathy and background retinopathy. Graefes Archive of Clinical and Experimental Ophthalmology 1990;28(6):505-9.	People with diabetes only, no retinopathy at baseline
Medi-Cal {published data only} California Medi-Cal Type 2 Diabetes Study Group. Closing the gap: effect of diabetes care management on glycemic control among low-income ethnic minority populations. Diabetes Care 2004;27(1):95-103.	People with diabetes only, no retinopathy at baseline
Pradhan R, Fong D, March C, Jack R, Rezapour G, Norris K, et al. Angiotensin-converting enzyme inhibition for the treatment of moderate to severe diabetic retinopathy in normotensive type 2 diabetic patients. A pilot study. Journal of Diabetes and Its Complications 2002;16(6):377-81.	People with diabetes only, no retinopathy at baseline
Rachmani R, Levi Z, Slavachevski I, Avin M, Ravid M. Teaching patients to monitor their risk factors retards the progression of vascular complications in high-risk patients with type 2 diabetes mellitus—a randomized	People with diabetes only, no retinopathy at baseline

Title	Reason for exclusion
prospective study. <i>DiabeticMedicine</i> 2002;19(5):385-92	
RASS Klein R, Moss SE, Sinaiko AR, Zinman B, Gardiner R, Suissa S, et al. The relation of ambulatory blood pressure and pulse rate to retinopathy in type 1 diabetes mellitus. <i>The Renin-Angiotensin System Study. Ophthalmology</i> 2006;113(12):2231-6.	People with diabetes only, no retinopathy at baseline
Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. <i>Annals of Internal Medicine</i> 1993;118(8):577-81	People with diabetes only, no retinopathy at baseline
ROADMAP Haller H, Ito S, Izzo JL, Januszewicz A, Katayama S, Menne J, et al for the ROADMAP Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. <i>New England Journal of Medicine</i> 2011;364(10):907-17 [with Supplementary Appendix]. [CTG: NCT00185159]	People with diabetes only, no retinopathy at baseline
Steno-2 Gaede J, Oellgaard J, Ibsen R, Gaede P, Nordestgaard E, Parving H-H, et al. A cost analysis of intensified vs conventional multifactorial therapy in individuals with type 2 diabetes: a post hoc analysis of the Steno-2 study. <i>Diabetologia</i> 2019;62:147-55. [CTG: NCT00320008] [DOI: 10.1007/s00125-017-4739-3]	People with diabetes only, no retinopathy at baseline
Wang N, Zheng Z, Jin HY, Xu X. Treatment effects of captopril on non-proliferative diabetic retinopathy. <i>Chinese Medical Journal</i> 2012;125(2):287-92.	People with diabetes only, no retinopathy at baseline
Zhao C-M, Cui X-L, Wan G, Lu Y-Z, Niu Y-Q, Su C-Y, et al. Analysis of the effect of nine consecutive years' intensive management and number of times achieving the target control on endpoint events in T2DM patients in Sanlitun Community Health Service Center in Beijing. <i>International Journal of Endocrinology</i> 2020;2020:Article ID 3646342. [DOI: 10.1155/2020/3646342]	People with diabetes only, no retinopathy at baseline

237 **Economic evidence**

Title	Reason for exclusion
Javitt, J C; Canner, J K; Sommer, A (1989) Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology 96(2): 255-64	Does not contain a population of people with Diabetic Retinopathy

238

239

## 240 **Appendix K - Research Recommendation**

### 241 **4.1.1 Research recommendation**

242 What is the effectiveness of intensive statin therapy compared with standard statin treatment  
243 for people with non-proliferative retinopathy and diabetic macular oedema?

### 244 **4.1.2 Why this is important**

245 Current evidence does not provide long-term follow up to ascertain the effectiveness of  
246 intensive statin therapy on diabetic retinopathy-related outcomes. While there is evidence to  
247 suggest that intensive statin therapy may have benefits in reducing the progression of  
248 diabetic retinopathy, there is currently limited long-term follow-up data available to fully  
249 assess its effectiveness and safety. Further research is needed to determine who would  
250 benefit most from intensive statin therapy and what the optimal dosing and duration is for this  
251 type of treatment. Additionally, studies should evaluate the acceptability, clinical  
252 effectiveness, cost-effectiveness, and potential adverse effects of intensive statin therapy  
253 over the long term.

### 244 **4.1.3 Rationale for research recommendation**

Importance to 'patients' or the population	Receiving appropriate medication is important to patients because treatment of disease can help prevent progression. It is also important to avoid prescribing to people if it is not beneficial.
Relevance to NICE guidance	The research is relevant to the recommendations in the guidance. Future research may provide more evidence on the longer-term effect of statins on progression of non-proliferative diabetic retinopathy and macular oedema.
Relevance to the NHS	Evidence on effectiveness of statin therapy could help clinicians to understand if the prescription of statins will help control people's diabetic retinopathy in the long term. This will help more people access the most effective treatments.
National priorities	Moderate
Current evidence base	Weak evidence was found to inform current recommendations in this area.
Equality considerations	It is unclear whether people from different ethnic backgrounds receive the same benefits from treatment as other people. This is important as these groups can be more at risk of developing severe forms of retinopathy.

255

### 246 **4.1.4 Modified PICO table**

Population	People with non-proliferative diabetic retinopathy and diabetic macular oedema
Intervention	Intensive statin therapy

Comparison	Standard statin therapy
Outcomes	<ul style="list-style-type: none"> <li>• Progression of retinopathy</li> <li>• Incidence of retinopathy</li> <li>• Incidence of macular ischemia</li> <li>• Changes in visual acuity</li> <li>• Vision-related health quality of life</li> <li>• Adverse events</li> <li>• Acceptability</li> </ul>
Study design	RCT
Timeframe	5-10 year follow up
Subgroups	<ul style="list-style-type: none"> <li>• People with hard exudates. / Without hard exudates</li> <li>• Type of diabetes</li> <li>• Pregnancy</li> <li>• Age</li> <li>• Ethnicity</li> </ul>

### 247 **1.5 Research recommendation**

258 What is the effectiveness of fibrates for the prevention of progression of diabetic retinopathy  
259 in people with different ethnicities.

### 260 **1.6 Why this is important**

261 People from certain ethnic backgrounds, such as people of African American, Hispanic and  
262 Native American descent, have been found to have a higher risk of developing diabetic  
263 retinopathy and experiencing more severe forms of the condition compared to people from  
264 other backgrounds. Therefore, it is important to understand whether fibrate therapy is equally  
265 effective for people of different ethnicities, as this information could inform personalised  
266 treatment decisions and improve health outcomes for individuals with diabetes.

### 267 **1.7 Rationale for research recommendation**

Importance to 'patients' or the population	Current evidence does not distinguish outcomes for people of different ethnicities who are known to be at higher risk of developing diabetes and therefore diabetic retinopathy
Relevance to NICE guidance	Current guidance can be stratified by ethnicity to provide more personalised recommendations. This will ensure that a wide range of people are benefiting as much as possible from the recommendations.
Relevance to the NHS	Evidence can inform more specific guidance for different demographics. It may provide better and more refined medication prescribing to ensure people have the best possible outcomes from treatment.
National priorities	Moderate

Current evidence base	No evidence has considered the effects of treatment for people of different ethnicities.
Equality considerations	This question is designed to address an equality consideration about the lack of evidence for people of certain ethnicities.

268

**10.1.8 Modified PICO table**

Population	People with non-proliferative diabetic retinopathy
Interventions	Fibrate therapy
Comparison	Placebo
Outcomes	<ul style="list-style-type: none"> <li>• Progression of retinopathy</li> <li>• Incidence of retinopathy</li> <li>• Incidence of macular ischemia</li> <li>• Changes in Visual acuity</li> <li>• Vision-related quality of life</li> <li>• Adverse events</li> </ul>
Study design	RCT
Timeframe	5-10 year follow up
Subgroups	<ul style="list-style-type: none"> <li>• Type of diabetes</li> <li>• Pregnancy</li> <li>• Age</li> <li>• Ethnicity</li> </ul>

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