National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring

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

NICE guideline NG242

Evidence reviews underpinning recommendations 1.1.6 to 1.1.9 and research recommendation 7 and 8 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-6431-4

Contents

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

Population	People with non-proliferative diabetic retinopathy
Interventions	Blood pressure control interventions (as described in Do et al. (2023): • Strict blood pressure control, alone or in combination with other interventions, when compared with less strict blood pressure control • Any blood pressure control, when compared with placebo • Any class of anti-hypertensive medicine compared with another class of anti-hypertensive medicine Fibrates (limited to those with a UK marketing authorisation): • Bezafibrate, ciprofibrate, gemfibrozil • Fenofibrate (as described in Cochrane review): (any dose/regimen) Statins: • Statin medications (for example atorvastatin, simvastatin) • Statins in combination with another lipid modification therapy or antihypertensive medication.
Comparator	Blood pressure control interventions (as described in Do et al. (2023)

	• Less strict blood pressure control when compared with strict blood pressure control. • Placebo • Another class of anti-hypertensive medicine when compared with a class of anti-hypertensive medicine. Fibrates • Placebo or observation (no treatment) Statins: • Fibrate (any dose/regimen) • Any blood pressure control intervention • Placebo or observation (no treatment)

Outcomes	• Visual acuity
	  ○ 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.
	  ○ 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)
	  ○ 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.
	• Incidence of proliferative diabetic retinopathy
	• Incidence of diabetic macular oedema
	• Incidence of diabetic macular ischaemia
	• Vision related quality of life (measured using validated tool)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual and the methods document for the diabetic retinopathy guideline.

Declarations of interest were recorded according to NICE's conflicts of interest policy. Methods specific to this review question are described in the review protocol in Appendix A.

This evidence review used data collected as part of 2 Cochrane reviews: Do et al. (2023) which assessed blood pressure interventions and Kataoka et al. (2023) which assessed the use of fenofibrate. Both studies were assessed as high quality and partially applicable to the review (see Appendix D). Information for these parts of the review were therefore used directly from the Cochrane reviews (see Table 2 in the methods document), rather than undertaking a new literature search. The reviews were considered partially applicable because they included a wider population than the population for this review (people with mild non-proliferative retinopathy or proliferative diabetic retinopathy at baseline). Because they included a wider population than in this review, an additional NICE search was not required.

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

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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies.

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

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

- For blood pressure control interventions, 6 studies that from were identified by the Cochrane review (Do et al. 2023) matched the inclusion criteria in this review protocol. All 6 compared blood pressure control to placebo.
- For statins, 5 studies from the NICE search matched the inclusion criteria and were included in this review. Three studies compared statins to placebo, 1 study compared statins plus fibrate to statins, and 1 study compared intensive statin therapy to standard statin therapy.
- For fenofibrate, 2 studies were identified by the Kataoka et al. 2023 Cochrane review and both matched the inclusion criteria in this review protocol. Both studies compared fenofibrate to placebo and reported outcomes for a subgroup of people with diabetic retinopathy at baseline.

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

For the full evidence tables and full GRADE profiles for included studies, please see Appendix D and Appendix F.

1.1.4.2 Excluded studies

See Appendix J for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Blood pressure control primary studies

See the Cochrane review (Do et al. 2023) for the full evidence tables for each of the studies for blood pressure control interventions. The 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	**Inclusion criteria:** • 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 • microvascular disease, current cigarette smoking, elevated total cholesterol (> 6.0 mmol/L), low HDL cholesterol (< 1.0 mmol/L), microalbuminuria • diagnosed with type 2 diabetes 10 years or more preceding entry into the study or age 65 years or older at recruitment. • an indication for an ACE inhibitor who enrolled at centres with retinal	• N= 623 • ACE inhibitor plus diuretic: Perindopril (2 mg) plus indapamide (0.625 mg) daily at randomization • doubled to perindopril (4 mg) plus indapamide (1.25 mg) after 3 months	• Placebo N=618	• progression of diabetic retinopathy ≥ 2 steps by ETDRS classification

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		cameras were eligible to participate. **Exclusion criteria for ADVANCE:** • definite indication or contraindication for the active study treatments or a definite indication for a HbA1c target of ≤ 6.5%, long-term insulin therapy at study entry or participating in a different clinical trial. **In addition, for ADVANCE/Amdram:** • previous ophthalmological intervention or inability to obtain good quality photographs due to either severe cataract or inadequate pupil dilation (< 4 mm)			
DIRECT Protect 1 30 countries; Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Germany, Greece,	RCT 4.8 years follow up	**Inclusion criteria:** • 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 • within a year of diagnosis, no microalbuminuria, SBP ≤ 130 mm Hg and DBP ≤ 85 mm Hg	• (N = 951) Angiotensin receptor antagonist only Candesartan cilexetil 16 mg (ARB) • Daily dose doubled or halved after one month; then doubled or halved based on tolerability	• (N = 954) placebo	• progression of retinopathy Secondary outcomes, as specified for this review: • progression to CSME and/or PDR per the ETDRS protocol

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, New Zealand, Poland, Portugal, Romania, Russian Federation, South Africa, Spain, Sweden, Turkey, United Kingdom		• and a diabetic retinopathy grading ≥ 20/10 (mild, non-proliferative), up to ≤ 47/47 • (Moderately severe non-proliferative) on the ETDRS scale based on 7-field stereo retinal photographs. **Exclusion criteria:** 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 ≥ 110 µmol/L for women and ≥ 130 µmol/L for men			
DIRECT Protect 2 Austria, Belgium, Croatia, Finland, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Romania, United Kingdom	RCT 2 years follow up.	**Inclusion criteria:** 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 ≤ 155 mm Hg	• (N=265) ACE inhibitor only 10 mg/day lisinopril,	• (N=265) Placebo	• 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 • progression to PDR

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		Exclusion criteria: renal artery stenosis, cardiac valve obstruction, accelerated hypertension, recent myocardial infarction, CABG, stroke, CHF, abnormal renal function (creatinine > 1.8 mg/dL), postural hypotension, or idiosyncratic reactions to ACE inhibitors			
Chew, 2014 (ACCORD) USA and Canada	RCT 4 years follow up	**Inclusion criteria:** 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. **Exclusion criteria**: People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded. NOTE: only outcomes for which a subgroup analysis of people with retinopathy at baseline were	(N = 314) The intensive treatment arm targeted systolic blood pressure <120 mmHg, N= for subgroup with diabetic retinopathy at baseline Microaneurysm or mild DR 1 eye, no DR or Ma only in other N= 173 Mild/moderate NPDR N=99 Moderate/moderately severe NPDR N=42	(N=330) The standard treatment arm targeted systolic blood pressure <140 mmHg. N= for subgroup with diabetic retinopathy at baseline) Microaneurysms or mild DR 1 eye, no DR or Ma only in other N=197 Mild/moderate NPDR N=95 moderate/moderately	• progression of DR (ETDRS)

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.		severe NPDR N=29	
JEDIT Japan (39 centres)	RCT 6 years follow up	**Inclusion criteria**: Age 65 - 85 years; HbA1c ≥ 7.9% OR 7.4% to < 7.9% AND BP > 130/85mmHg: other criteria related to cholesterol, etc. **Exclusion criteria**: VA < 20/200 and history of glaucoma; if grading of the ocular fundus was not possible, eye was excluded from analysis of DR ("940 eyes of 940 participants met the inclusion criteria"); if MI or stroke in < 6 months, excluded	• (N = 588) Intensive BP monitoring: goals: HbA1c < 6.9%; BMI < 25 kg/m2; BP <130/85 mm Hg; HDL-C > 40 mg/dL; serum triglycerides < 150 mg/dL, serum total cholesterol< 120 mg/dL for participants without CHD. • For participants with CHD: LDL-C < 100 mg/dL • Physicians prescribed oral hypoglycaemic drugs or insulin and atorvastatin to achieve targets.	(N = 585) Conventional BP monitoring: usual baseline treatment for diabetes, hypertension, and dyslipidaemia without special treatment goals, i.e., no intervention	• progression of DR
UKPDS/HDS United Kingdom	RCT 9.3 Year follow up	**Inclusion criteria:** Type 2 diabetes and participating in the UKPDS, mean of blood pressure readings from 3 consecutive visits > 160 mm Hg SBP and/or a DBP > 90 mm Hg when not receiving treatment for hypertension or SBP > 150 mm	• LTBP control policy aiming for blood pressure < 150/85 mm Hg; random allocation to either ACE inhibitor or a beta-blocker.	LTBP control policy aiming for blood pressure ≤ 180/105 mm Hg but avoiding therapy with ACE inhibitors or beta-blockers.	• progression of retinopathy defined as a 2-step or greater change by ETDRS grading. • visual loss defined as the best vision in either eye, deteriorating by 3 lines or

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		Hg and/or a DBP > 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. **Exclusion criteria:** Requirement for strict blood pressure control due to a previous stroke, accelerated hypertension, ketonuria > 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; contraindication to beta-blockade (with conditions such as asthma, intermittent claudication, foot ulcers or amputations); and severe concurrent illness.	• captopril (ACE inhibitor) starting at 25 mg twice daily, increasing to 50 mg twice daily. • Atenolol (beta-blocker) starting at 50 mg daily, increasing to 100 mg daily. • 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 (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		more on the ETDRS chart (clinical records); • progression to PDR or photocoagulation

Table 3: Statins primary studies

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Gupta, 2004 India	RCT 18 week follow up	**Inclusion criteria:** 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 **Exclusion criteria:** People with macular ischemia, pseudophakia, poorly controlled hypertension, associated vascular occlusions, media opacities, debilitating systemic diseases, coronary artery diseases, and any	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)	• visual acuity • progression of DR (macular oedema, distribution of hard exudates)

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		hepatic or muscular diseases were excluded from the study, as were pregnant patients			
Murakami, 2021 Japan	RCT – A prespecified ophthalmology subgroup 3 years follow up	**Inclusion criteria:** 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§ ≥120 mg/dL for previously untreated patients or ≥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 ± 3 months) were eligible for participation in sub study **Exclusion criteria**: 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	Intervention: (N =85) Patients were randomly assigned to oral intensive statin therapy (targeting LDL-C below 70 mg/dL)	Comparator: (N =72) standard statin therapy (targeting LDL-C between 100 and 120 mg/dL), placebo	• Incidence of DR (ETDRS) • Visual acuity (Logarithm of the Minimum Angle of Resolution, LogMAR)

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		revascularization),Symptomatic PAD, Uncontrolled hypertension with DBP ≥ 120 mmHg or SBP ≥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			
Narang, 2012 India	RCT 6 months follow up	**Inclusion criteria**: People with non-proliferative diabetic retinopathy (NPDR) with CSM, 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.	Intervention: (N =15) Group A patients were administered Atorvastatin (daily dose of 20 mg) throughout the study period starting four weeks prior to laser treatment.	Comparator: (N =15) Group B patients were given placebo during study period	• Visual acuity • Progression of DR (distribution of hard exudates)

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		Exclusion criteria: 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.			
Sen, 2007	RCT	**Inclusion criteria:**	Intervention: (N =25) simvastatin 20-mg per day	Comparator: (N =25) placebo	• Incidence of DR (macular oedema)

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
	3 month follow up	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: 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). 2. VA 6/24 or better in one or both eyes. 3. Leaking capillaries, intra-retinal microvascular abnormalities (IRMAs), and/or microaneurysms at least 500 away from fovea in one or both eyes. 4. No laser photocoagulation in last year. 5. Absence of clinically significant macular oedema (CSME), proliferative DR, age-related			• Visual acuity

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

Table 4: Fibrates primary studies

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	**Inclusion criteria:** 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 Islanders, the eligible age of diagnosis was >25 years, provided there had been at least 1 year of treatment without insulin.	Oral fenofibrate, 200mg/day (n=512) Retinopathy at baseline Overt retinopathy,105 (20.5%) DR status none, 407 (79.5%) DR status mild, 88 (17.2%) DR status moderate NPDR, 14 (2.7%)	Placebo (n=500) Retinopathy at baseline Overt retinopathy, 103 (20.6%) DR status none, 397 (79.4%) DR status mild, 78 (15.6%) DR status moderate NPDR, 21 (4.2%)	Reported for subpopulation with diabetic retinopathy at baseline: • Progression of DR • Only reported for whole population so not included in this review: • Incidence of overt retinopathy • Incidence of DMO • Laser treatment • Vitrectomy

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		3. On the basis of diabetes, considered to be at higher risk for coronary heart disease than the general population 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. 5. T-chol level 3 to 6.5 mmol/L, plus either 6. A T-chol-to-HDL cholesterol ratio of ≥ 4.0 7. A blood triglyceride level >1.0 mmol/L 8. No clear contraindication to study therapy in the view of the treating physician 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. 10. Two-field colour fundus photographs of both eyes showed no evidence of PDR, severe NPDR,	DR status severe NPDR,3 (0.6%),	DR status severe NPDR, 4 (0.8%)	

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		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. **Exclusion criteria:** Individuals were not eligible if they had any of the following characteristics: 1. Serum triglyceride >5 mmol/L in the baseline visit fasting blood sample 2. Concurrent treatment with any other lipid-lowering agent 3. Serum creatinine >130 µmol/L 4. Known chronic liver disease, transaminases >2 × upper limit of normal or symptomatic gallbladder disease 5. MI or hospital admission for unstable angina within 3 months 6. Female, of child-bearing potential, unless sterilized or on reliable approved methods of contraception, including oral contraceptives. 7. Concurrent cyclosporin treatment (or a condition likely to result in organ transplantation and			

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		the need for cyclosporin during the next 5 years) 8. Known allergy to any fibrate drug or known photosensitivity 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. 10. A number of other ocular pathologies or technical problems NOTE: Data was only included in this review for outcomes that were reported for people with diabetic retinopathy at baseline			
Chew, 2014 (ACCORD) USA and Canada	RCT 4 years follow up	**Inclusion criteria:** 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. **Exclusion criteria**: People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated	(N = 806, N=399 for subgroup with diabetic retinopathy at baseline) Fenofibrate 160 mg/day plus simvastatin Ma or mild DR 1 eye, no DR or Ma only in other N=264 mild/moderate NPDR N=88 moderate/moderately severe NPDR N=47	(N=787, N=402 for subgroup with diabetic retinopathy at baseline) Placebo plus simvastatin Ma or mild DR 1 eye, no DR or Ma only in other N=258 mild/moderate NPDR N=104 moderate/moderately	• Progression of DR (ETDRS)

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		with laser photocoagulation or vitrectomy were excluded. 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.		severe NPDR N=40	

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

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

Blood pressure control interventions

More blood pressure control vs less blood pressure control

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

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

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.

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

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[1]	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					

Statins interventions

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

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.

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

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^2 >33%					

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					

Intensive statin therapy vs standard statin therapy

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)					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Murakami 2020	RCT	128	Risk Ratio: 0.98 [0.40, 2.37]	Moderate[1]	Could not differentiate
1 Partially applicable Mixed population with 50% population with proliferative disease					

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

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[1]	Could not differentiate
1 Partially applicable Mixed population with 50% population with proliferative disease					

Fibrates interventions

Fenofibrate compared to placebo

Table 15: 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).

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

Table 16: Statins plus fenofibrate vs Statin: 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 (RR<1 favours fenofibrate)					
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 Fenofiibrate)					
1	RCT	522	Risk Ratio: 0.30 [0.14, 0.65]	Low	Favours statins plus fibrate

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subgroup: mild/moderate NPDR) (RR<1 favours fenofibrate)					
1	RCT	192	Risk Ratio:0.51 [0.20, 1.26]	Low	Could not differentiate
Subgroup: moderate/moderately severe NPDR) (RR<1 favours Fenofibrate)					
1	RCT	87	Risk Ratio: 0.51 [0.20, 1.28]	Low	Could not differentiate

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies.

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

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

See the health economic study selection flow chart presented in Appendix G.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified to be included.

1.1.9 Economic model

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

1.1.10 Unit costs

Table 17: Unit costs

Resource	Unit cost	Source
Atorvastatin 20mg	£0.91	British National Formulary (25/09/2023) pack of 28 tablets.
Fenofibrate 160mg	£3.27	British National Formulary (25/09/2023) pack of 28 tablets.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

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

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

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

1.1.11.2. The quality of the evidence

Blood pressure control

Six studies were identified for people with non-proliferative retinopathy who were eligible for intensive blood pressure treatment. The evidence for each outcome ranged from moderate to high quality. Most studies were downgraded for indirectness as a large proportion of participants were people with mild diabetic retinopathy. These people would be treated outside of hospital eye services and so are not directly relevant to the scope of this guideline. However, the committee agreed that the evidence was still useful.

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

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

Statins

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

Fibrates

Two studies were identified that reported on a subgroup of people with non-proliferative diabetic retinopathy at baseline. The ACCORD-Lipid and FIELD studies were two large randomized clinical trials that investigated the effect of lipid-lowering therapies on cardiovascular outcomes in individuals with type 2 diabetes, but also reported on retinopathy-related outcomes. The quality of the evidence for each outcome was low. Evidence was downgraded for risk of bias due to selective reporting of outcomes and indirectness, because a large proportion of the participants in the subgroup had mild diabetic retinopathy. No evidence was available for the other outcomes included in the review protocol. There were no studies identified for other fibrates, although the committee were aware of ongoing clinical trials for the effectiveness of fibrates for people with type 1 diabetes. **Imprecision and the clinical importance of effects**

The committee agreed that for most outcomes, the evidence on blood pressure control medicines and fenofibrate was precise enough to draw conclusions from the evidence. They considered that the effects of blood pressure control in the subgroup with hypertension was likely to be clinically important. The evidence on statins was from trials with a small number

of participants, resulting in wide confidence intervals. The committee were therefore limited on the conclusions that could be drawn from this evidence.

1.1.11.3 Benefits and harms

Blood pressure control

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

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

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

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

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

Statins

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

Most outcomes did not show a clear benefit of statins over placebo. There was some evidence of a benefit in visual acuity measured at 18 weeks, though most of the studies that reported on this outcome were from a population who had non-proliferative retinopathy with diabetic macular oedema or clinically significant macular oedema. Given this limited evidence, the committee did not think they could make specific recommendations on the use of statins for diabetic retinopathy.

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

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

Fibrates

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

The committee also reviewed evidence from the ACCORD study stratified by severity of retinopathy at baseline. The evidence showed that for the subgroup of people with very mild diabetic retinopathy, fenofibrate slowed progression of retinopathy at 5 years. Similarly, for people with mild or moderate and moderate to moderately severe non-proliferative diabetic retinopathy, the overall effect showed a benefit of fenofibrate on reducing progression of retinopathy, however, the committee were in agreement that the wider confidence intervals could be due to the small numbers in these groups and there was no evidence of a difference across subgroups. The FIELD Eye study demonstrated that treatment with fenofibrate was effective in reducing the risk of progression of diabetic retinopathy and the need for laser treatment for diabetic retinopathy.

The committee agreed that both studies provide valuable insights into the potential benefits of lipid-lowering therapies for the management of diabetic retinopathy in individuals with type 2 diabetes and so they decided to recommend the use of fenofibrate for people with non-

proliferative diabetic retinopathy and type 2 diabetes. They were aware that this is currently an off-label use of fenofibrate, and so they thought that ophthalmologists should be the first to consider prescribing fenofibrate, which will then encourage GPs to continue to prescribe them. The majority of the evidence was for people with type 2 diabetes, and the committee did not think they could extrapolate this information to people who have type 1 diabetes. However, they were aware of an ongoing clinical trial for the use of fibrates for people with type 1 diabetes which could be used to make recommendations in the future.

The committee discussed the lack of evidence on the effects of other fibrates for people from a range of ethnic backgrounds who are at high risk of developing diabetes and diabetic retinopathy. They therefore made a research recommendation about the effectiveness of fibrates in these groups (see Appendix K).

1.1.11.4 Cost effectiveness and resource use

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

Blood pressure control

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

Statins

No resource impact is expected because the committee did not make a recommendation for statins.

Fibrates

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

1.1.11.5 Other factors the committee took into account.

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

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6 to 1.1.9and the research recommendations on intensive statin therapy for people with non-proliferative retinopathy and diabetic macular oedema and fibrates for the prevention of progression of diabetic retinopathy in people with different ethnicities.

1.1.13 References – included studies

1.1.13.1 Clinical evidence – systematic reviews

Do et al. (2023). Do DV, Han G, Abariga SA, Sleilati G, Vedula SS, Hawkins BS. Blood pressure control for diabetic retinopathy. Cochrane Database of Systematic Reviews 2023, Issue 3. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

1.1.13.1 Clinical evidence – primary studies

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

Included studies from Antihypertensives Cochrane review: Do et al 2023

ACCORD Eye {published data only}

Action to Control Cardiovascular Risk in Diabetes FollowOn (ACCORDION) Eye Study Group and Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent eCects 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 2016;39:10889-1100. [DOI: 10.2337/dc16-0024]

ADVANCE/AdRem {published data only}

ADVANCE Collaborative Group. ADVANCE - Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline. Diabetic Medicine 2005;22(7):882-8.

ADVANCE Collaborative Group. ECects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370(9590):829-40.

ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 2008;358(24):2560-72.

ADVANCE Management Committee. Study rationale and design of ADVANCE: Action in Diabetes and Vascular Disease - preterax and diamicron MR controlled evaluation. Diabetologia 2001;44(9):1118-20.

DIRECT Protect 1 {published data only}

Chaturvedi N, DIRECT Programme Study Group. DIabetic REtinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. Journal of the Renin-Angiotensin-Aldosterone System 2002;3(4):255-61.

* Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, et al. ECect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of

retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet 2008;372(9647):1394-402.

DIRECT Programme Study Group. DIabetic REtinopathy Candesartan Trials (DIRECT) Programme: baseline characteristics. Journal of the Renin-Angiotensin-Aldosterone System 2005;6(1):25-32.

DIRECT Protect 2 {published data only}

Chaturvedi N, DIRECT Programme Study Group. DIabetic REtinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. Journal of the Renin-Angiotensin-Aldosterone System 2002;3(4):255-61.

DIRECT Programme Study Group. DIabetic REtinopathy Candesartan Trials (DIRECT) Programme: baseline characteristics. Journal of Renin-Angiotensin-Aldosterone System 2005;6(1):25-32.

* Sjolie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, et al. ECect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet 2008;372(9647):1385-93

J-EDIT {published data only}

Araki A, Iimuro S, Sakurai T, Umegaki H, Iijima K, Nakano H, et al. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial–study design, baseline characteristics and eCects of intervention. Geriatrics & Gerontology International 2012;12:7-17.

Tanaka S, Yoshimura Y, Kawasaki R, Kamada C, Tanaka S, Horikawa C, et al. Fruit intake and incident diabetic retinopathy with type 2 diabetes. Epidemiology 2013;24(2):204-11. [PMID: 23348071]

Yamamoto T, Iimuro S, Ohashi Y Sone H, Yamashita H, Ito H, Japanese Elderly Intervention Trial Research Group. Prevalence and risk factors for diabetic maculopathy, and its relationship to diabetic retinopathy in elderly Japanese patients with type 2 diabetes mellitus. Geriatrics and Gerontology International 2012;12:134-40

UKPDS/HDS {published data only}

Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al. UKPDS 50: Risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia 2001;44(2):156-63.

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837-53.

UK Prospective Diabetes Study Group. Cost eCectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. BMJ 1998;317(7160):720-6

Included studies from fibrates Cochrane review. Kataoka et al. 2023

ACCORD-Lipid {published data only}

ACCORD Study Group, Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, et al. Action to control cardiovascular risk in diabetes (ACCORD) trial: design and methods. American Journal of Cardiology 2007;99(12):S21-33.

ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Eects of combination lipid therapy in type 2 diabetes mellitus. New England Journal of Medicine 2010;362(17):1563-74.

ACCORD Study Group, ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. New England Journal of Medicine 2010;363(3):233-44.

Chew EY, Ambrosius WT, Howard LT, Greven CM, Johnson S, Danis RP, et al. Rationale, design, and methods of the action to control cardiovascular risk in diabetes eye study (ACCORD-EYE). American Journal of Cardiology 2007;99(Suppl 12):S103-11.

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

FIELD {published data only}

D'Emden M, Li LP, Zannino D, Best J, Keech AC, on behalf of the FIELD Study Investigators . EDect of fenofibrate on cardiovascular events and mortality in women with type 2 diabetes: results from the fenofibrate intervention and event lowering in diabetes (FIELD) study. Diabetes 2009;58(Suppl 1A):A178.

FIELD Study Investigators. The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. [ISRCTN64783481]. Cardiovascular Diabetology 2004;3(9):1-11.

Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366(9500):1849-61.

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

Scott R, Best J, Forder P, Taskinen MR, Simes J, Barter P, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: baseline characteristics and short-term eDects of fenofibrate [ISRCTN64783481]. Cardiovascular Diabetology 2005;4(13):1-9.

Statins

Chew, Emily Y, Davis, Matthew D, Danis, Ronald P et al. (2014) 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 121(12): 2443-51

Gupta, Amod, Gupta, Vishali, Thapar, Shveta et al. (2004) Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. American journal of ophthalmology 137(4): 675-82

Murakami, Tomoaki, Kato, Satoshi, Shigeeda, Takashi et al. (2021) Intensive treat-to-target statin therapy and severity of diabetic retinopathy complicated by hypercholesterolaemia. Eye (London, England) 35(8): 2221-2228

Narang, S, Sood, S, Kaur, B et al. (2012) Atorvastatin in clinically significant macular edema in diabetics with a normal lipid profile. Nepalese journal of ophthalmology : a biannual peer-reviewed academic journal of the Nepal Ophthalmic Society : NEPJOPH 4(1): 23-8

Sen, Kaushik, Misra, Anoop, Kumar, Atul et al. (2002) Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia. Diabetes research and clinical practice 56(1): 1-11

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	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. Two Cochrane reviews have been identified which partially cover this question: https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full 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. 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.

4.	Searches	Studies from the following Cochrane reviews will be considered for inclusion: https://www.cochrane.org/CD013318/EYES_fenofibrate-diabetic-retinopathy https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006127.pub2/full A systematic search will be conducted to cover the fibrates other than fenofibrates and statins , which are not covered by existing Cochrane reviews: The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records) • INAHTA • MEDLINE • Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA

		Searches will be restricted by: • Studies reported in English • Study design RCT will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit will be set unless specified by the protocol • Cost Utility (specific) and Cohort Studies for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	Inclusion: People diagnosed with non-proliferative diabetic retinopathy 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.
7.	Intervention	Blood pressure control interventions (as described in Cochrane review): • Strict blood pressure control, alone or in combination with other interventions, when compared with less strict blood pressure control • Any blood pressure control, when compared with placebo • Any class of anti-hypertensive medicine compared with another class of anti-hypertensive medicine Fibrates (limited to those with a UK marketing authorisation):

		• Bezafibrate, ciprofibrate, gemfibrozil • Fenofibrate (as described in Cochrane review): (any dose/regimen) Statins: • Statin medications (for example atorvastatin, simvastatin) • Statins in combination with another lipid modification therapy or antihypertensive medication.
8.	Comparator	Blood pressure control interventions (as described in Cochrane review): – Less strict blood pressure control when compared with strict blood pressure control – Placebo – Another class of anti-hypertensive medicine when compared with a class of anti-hypertensive medicine Fibrates: – Placebo or observation (no treatment) Statins: – Fibrate (any dose/regimen) – Any blood pressure control intervention – Placebo or observation (no treatment)
9.	Types of study to be included	Randomised controlled trials
10.	Other exclusion criteria	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). Studies comparing different doses of medicines only will be excluded.
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom.

12.	Primary outcomes (critical outcomes)	• 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)

13.	Secondary outcomes (important outcomes)	• Visual acuity
		  ○ 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
		  ○ 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)
		  ○ 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.
		• Incidence of proliferative diabetic retinopathy
		• Incidence of diabetic macular oedema
		• Incidence of diabetic macular ischaemia
		• Vision related quality of life (measured using validated tool)
		
		Applies to primary and secondary outcomes:
		• Outcomes will be reported at the latest time point reported by the study.
		• As the review is investigating the effectiveness of systematic treatments, the unit of analysis will be the individual participant.
		• 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.

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 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. 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.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool. 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.
16.	Strategy for data synthesis	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. 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. 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). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, when random effects models will be used instead. 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.
17.	Analysis of sub-groups	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. Data will be presented separately for the following groups: • Pregnant women If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Socioeconomic status • Type 1 diabetes vs type 2 diabetes
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ 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	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑ ☑	☑ ☑
		Piloting of the study selection process	☐ ☐	☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐	☐ ☐
		Data extraction	☐ ☐	☐ ☐
		Risk of bias (quality) assessment	☐ ☐	☐ ☐
		Data analysis	☐ ☐	☐ ☐
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** diabeticretinopathy@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Syed MohiuddinHannah Lomax • Kirsty Hounsell • Jenny Craven • Jenny Kendrick		

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 Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • 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.
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	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

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

Database: 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*))):ti,ab,kw 5557
#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 fluindostatin* 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

Database: 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 fluindostatin/ or pravastatin/ or rosuvastatin/	84101
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.	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 lopid*) OR abstract:(gemfibrozil* OR lopid*)) 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 fluindostatin* 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 lopid*).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 filer 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

Database	Date searched	Database Platform	Database segment or version
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 rwanda/ 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 rwanda/ 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

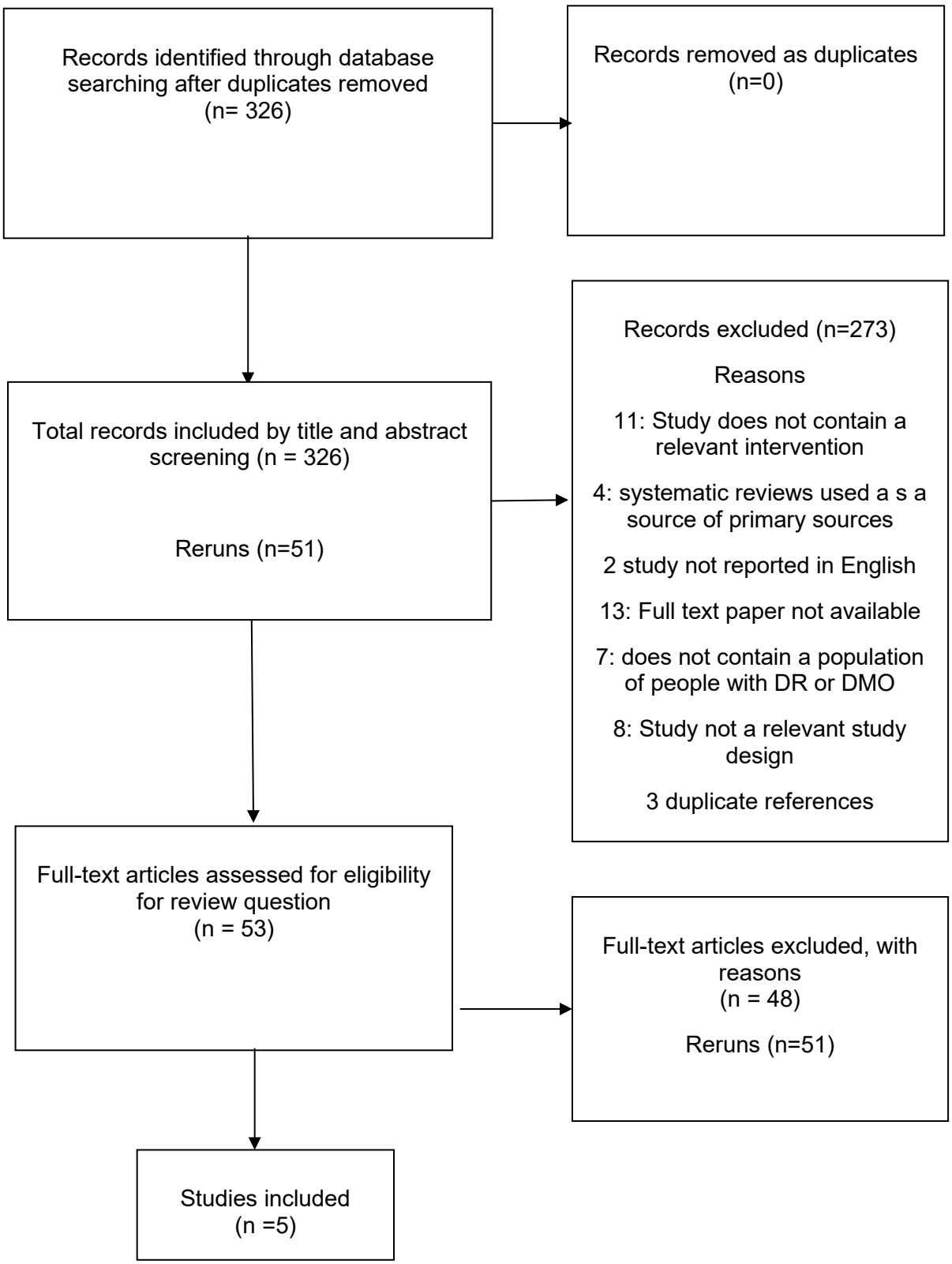
Appendix C – Effectiveness evidence study selection

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


Records identified through database searching after duplicates removed (n= 326)
Records removed as duplicates (n=0)
Total records included by title and abstract screening (n = 326)
Reruns (n=51)
Records excluded (n=273)
Reasons
11: Study does not contain a relevant intervention
4: systematic reviews used a s a source of primary sources
2 study not reported in English
13: Full text paper not available
7: does not contain a population of people with DR or DMO
8: Study not a relevant study design
3 duplicate references
Full-text articles assessed for eligibility for review question (n = 53)
Full-text articles excluded, with reasons (n = 48)
Reruns (n=51)
Studies included (n =5)

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.

Appendix D – Effectiveness evidence

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

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)

Study Characteristics

Study design	Systematic review
Study details	Dates searched. Last searched on 3 September 2021 Databases searched. • 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) • MEDLINE Ovid (1946 to 3 September 2021)

	• Embase.com (1947 to 3 September 2021) • Latin American and Caribbean Health Sciences Literature database (LILACS) (1982 to 3 September 2021) • US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; searched 3 September 2021) • World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registryplatform; searched 3 September 2021) Sources of funding 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.
Inclusion criteria	Type of studies Randomised controlled trials Type of participants 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. Type of interventions Trials in which:

	• 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; • participants assigned to blood pressure control were compared with participants assigned to usual care or no intervention on blood pressure (placebo); • participants assigned to antihypertensive agents versus placebo; • participants assigned to treatment with one class of antihypertensive agent were compared with participants assigned to another class of antihypertensive agent.
Exclusion criteria	No exclusion criteria were listed in the section of methods
Intervention(s)	Antihypertensive medication Placebo
Outcome(s)	Visual acuity Incidence of proliferative diabetic retinopathy Incidence of diabetic macular oedema Vision related quality of life
Number of studies included in the systematic review	29 RCTs
Studies from the systematic review that are relevant for use in the current review	ACCORD ADVANCE/AdRem DIRECT Protect 1

	DIRECT Protect 2 JEDIT UKPDS/HDS
Studies from the systematic review that are not relevant for use in the current review	• These studies were excluded because they included people who had diabetes with no retinopathy at baseline. • ABCD (1) • ABCD (2) • ABCD-2V (1) • AdDIT • ADDITION-Europe • BENEDICT • Chase • DEMAND • DIRECT Prevent 1 • EUCLID • HINTS • J-DOIT3 • Knudsen • Larsen • Medi-Cal • Pradhan • Rachmani 2002 • RASS • Ravid 1993 • ROADMAP • Steno-2 • Wang • Zhao

Additional comments	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.

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 *(ACCORD included population with proliferative retinopathy at baseline)*

D.2 Statins

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

Study details

Trial registration number and/or trial name	NCT00542178 for the ACCORD Eye study.
Study type	Randomised controlled trial (RCT)
Study location	USA and Canada
Study setting	Not reported
Study dates	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.
Sources of funding	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 pharmaceutics companies
Inclusion criteria	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.
Exclusion criteria	People who, at baseline, had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded.
Intervention(s)	Group 1: fenofibrate 160 mg/day plus simvastatin (n =806)
Comparator	Group 2: placebo plus simvastatin (n =787)
Number of participants	1593

Duration of follow-up	4 years
Loss to follow-up	(82.3%) participants had both baseline and year 4 follow-up data available for analyses
Additional comments	Type 2 diabetes, moderate dyslipidaemia, established cardiovascular disease or cardiovascular risk factors (n =1594)
Baseline characteristics	Age (yr) 61.6 (6.3) Female:501 Diabetes Duration (yr) 10.0 (7.1)

Study arms

Simvastatin plus fenofibrate (N = 806) 160 mg daily of fenofibrate plus simvastatin

Simvastatin plus Placebo (N = 787) placebo plus simvastatin

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

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

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Retina Clinic of tertiary-care referral institute.
Study dates	Not reported
Sources of funding	not detailed
Inclusion criteria	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
Exclusion criteria	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.

Intervention(s)	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. 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)
Comparator	In group B, 15 patients were subjected to metabolic control but did not receive any lipid-lowering therapy 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)
Outcome measures	Visual acuity Progression of DR (macular oedema, distribution of hard exudates)
Number of participants	Non-proliferative diabetic retinopathy with clinically significant macular oedema (n =30)
Duration of follow-up	18 weeks
Loss to follow-up	0 lost to follow up
Baseline characteristics	Age (yr.): **atorvastatin:**55.53 (8.29) **placebo** 52.73 (7.27) Sex, M:F **atorvastatin** 10:5 **placebo** 11:4

Study arms

Atorvastatin (N = 15) Group 1: atorvastatin 10 mg/day both groups received also Nd Yag Green laser (532 Nm)

Placebo (N = 15) Group 2: no intervention (n=15) Both groups received also Nd Yag Green laser (532 Nm)

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

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

Study details

Secondary publication of	a prespecified ophthalmology sub study of the EMPATHY study, which used a multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) design

another included study- see primary study for details	
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	ophthalmology departments at prevention sites (hospitals and clinics)
Study dates	between May 2010 and October 2013.
Sources of funding	supported by Shionogi & Co., Ltd.
Inclusion criteria	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§ ≥120 mg/dL for previously untreated patients or ≥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 ± 3 months) were eligible for participation in sub study
Exclusion criteria	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 ≥ 120 mmHg or SBP ≥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
Intervention(s)	Patients were randomly assigned to oral intensive statin therapy (targeting LDL-C below 70 mg/dL)

Comparator	standard statin therapy (targeting LDL-C between 100 and 120 mg/dL),
Outcome measures	Incidence of DR (ETDRS) Visual acuity (Logarithm of the Minimum Angle of Resolution, LogMAR)
Number of participants	219
Duration of follow-up	36 ± 3 months

Study arms

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

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

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

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

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Retina services of our institute which is a tertiary eye care centre.
Sources of funding	not detailed
Inclusion criteria	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.
Exclusion criteria	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.
Intervention(s)	Group A patients were administered Atorvastatin (daily dose of 20 mg) throughout the study period starting four weeks prior to laser treatment.

Comparator	Group B patients were given placebo during study period.
Outcome measures	Visual acuity Progression of DR (distribution of hard exudates)
Number of participants	30
Duration of follow-up	All patients had minimum of six months follow up. The follow up was scheduled at three monthly intervals
Loss to follow-up	0
Methods of analysis	Both the groups were compared using unpaired t test for quantitative parameters and chi square test for qualitative parameters.
Baseline characteristics	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

Study arms

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

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

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

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

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Sources of funding	Provision of tablets of simvastatin and placebo from Ranbaxy Laboratories
Inclusion criteria	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:

	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). 2. VA 6/24 or better in one or both eyes. 3. Leaking capillaries, intra-retinal microvascular abnormalities (IRMAs), and/or microaneurysms at least 500 away from fovea in one or both eyes. 4. No laser photocoagulation in last year. 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.
Exclusion criteria	People showing either mild background DR or proliferative DR or CSME was excluded
Intervention(s)	simvastatin 20-mg per day
Comparator	placebo
Outcome measures	Incidence of DR (macular oedema) Visual acuity
Number of participants	50
Duration of follow-up	3 months
Loss to follow-up	A total of 133 patients were evaluated, and 50 recruited for the study all 50 were analysed

Baseline characteristics	Mean (S.D.) age were 54.9 (7.8) and 53.0 (10.2) years in the simvastatin and placebo groups

Study arms

simvastatin 20 mg/day (N = 25)

placebo (N = 25)

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

D.3 Fibrate

This part of the review question was answered by using a recently published Cochrane review Kataoka et al 2023.

Details of the study selection, evidence tables and risk of bias assessments can be found in the published Cochrane review. Additionally, . 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 in the table below.

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

Study Characteristics

Study design	Systematic review
Study details	Dates searched. The date of the search was 1 February 2022. Databases searched. • 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) • MEDLINE Ovid (1946 searched 1 February 2022) • Embase Ovid (1980 searched 1 February 2022) • ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 1 February 2022) • US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 1 February 2022) • World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 1 February 2022) Sources of funding 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 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. 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.

Inclusion criteria	Type of studies Randomised controlled trials Type of participants 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. Type of interventions Intervention: fenofibrate (any dose/regimen) Comparison: placebo or observation
Exclusion criteria	Type of studies Post-trial follow-up studies Type of participants Studies including only participants with established complications of diabetic retinopathy (i.e. diabetic macular oedema/proliferative diabetic retinopathy) were excluded.
Intervention(s)	Placebo Fenofibrate
Outcome(s)	Visual acuity

	Incidence of proliferative diabetic retinopathy Incidence of diabetic macular oedema Vision related quality of life
Number of studies included in the systematic review	2 RCTs
Studies from the systematic review that are relevant for use in the current review	ACCORD FIELD
Studies from the systematic review that are not relevant for use in the current review	None - all are relevant and included in the NICE review

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low

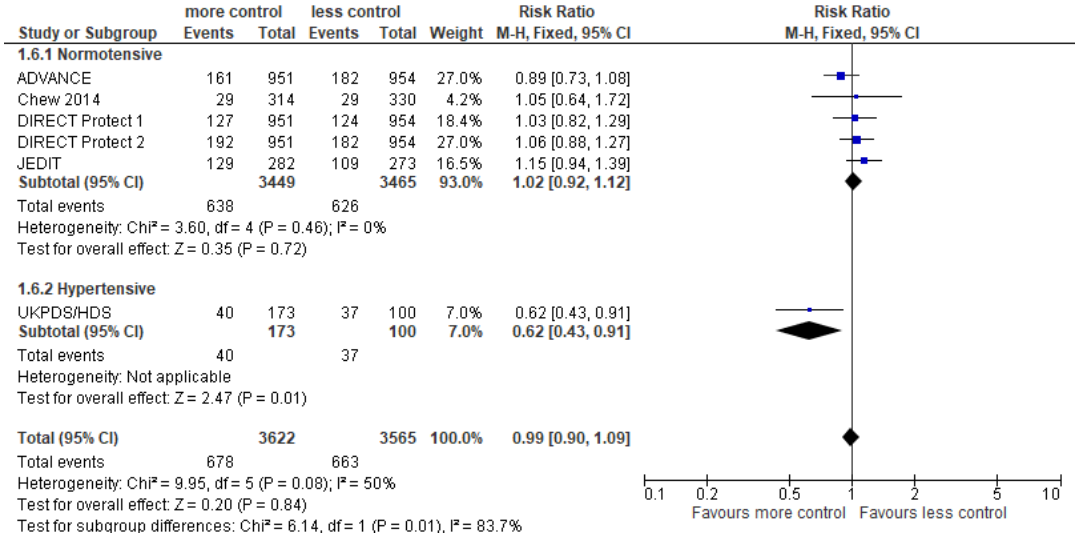
Section	Question	Answer
Overall study ratings	Applicability as a source of data	Partially applicable *(Subgroup with diabetic retinopathy included a large proportion (>50%) with mild non-proliferative retinopathy. FIELD study included population with proliferative retinopathy at baseline.)*

Appendix E – Forest Plots

E.1 Blood pressure control interventions

More blood pressure control versus less blood pressure control

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



Sensitivity analysis

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.

Study or Subgroup	more control Events	Total	less control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Normotensive						
ADVANCE	161	951	182	954	35.2%	0.89 [0.73, 1.08]
Chew 2014	29	314	29	330	5.5%	1.05 [0.64, 1.72]
DIRECT Protect 1	127	951	124	954	24.0%	1.03 [0.82, 1.29]
DIRECT Protect 2	192	951	182	954	35.2%	1.06 [0.88, 1.27]
Subtotal (95% CI)		**3167**		**3192**	**100.0%**	**0.99 [0.89, 1.11]**
Total events	509		517			

Heterogeneity: Chi² = 1.92, df = 3 (P = 0.59); I² = 0%

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable

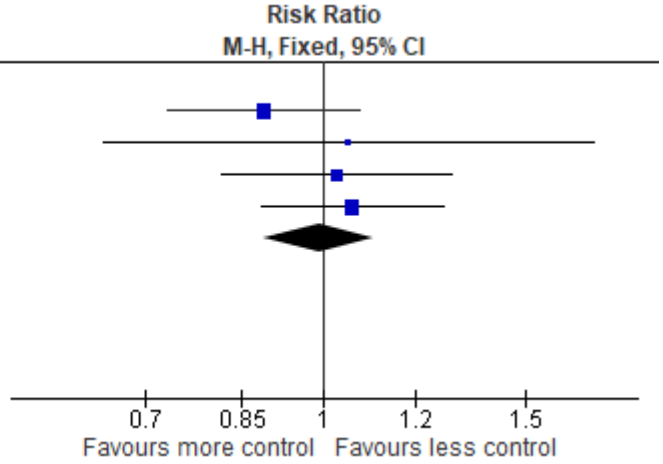


Figure 3: Five-year Progression to Proliferative Diabetic Retinopathy, Clinically Significant Macular oedema, or vitreous haemorrhage

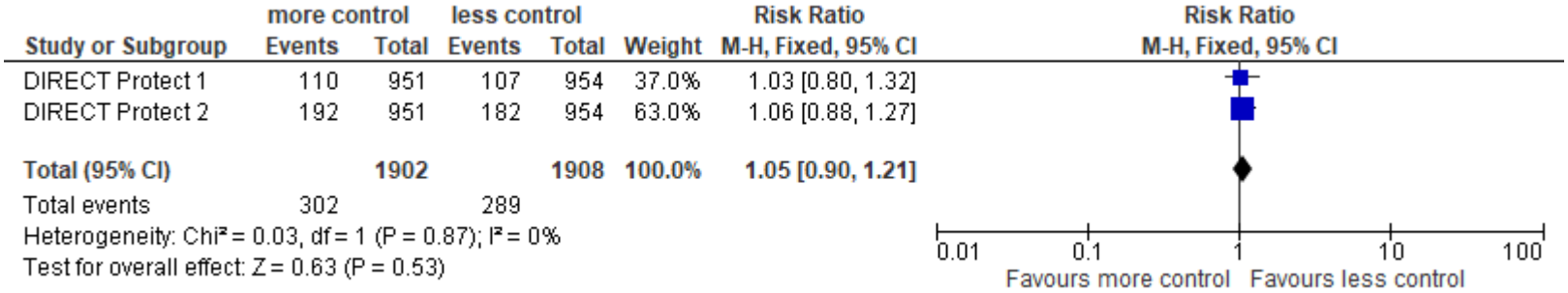


Figure 4: Progression of diabetic retinopathy by 7 to 9 years

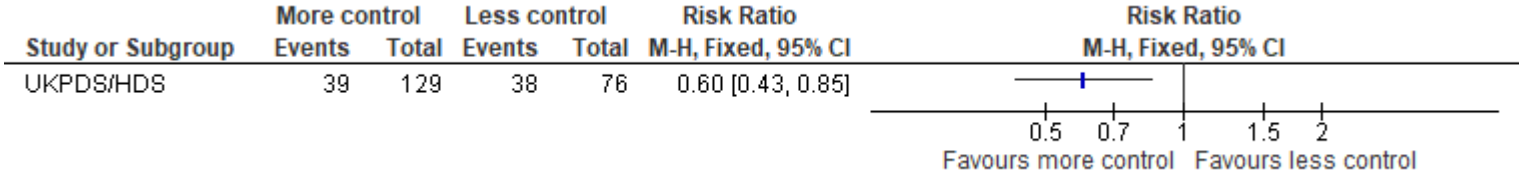
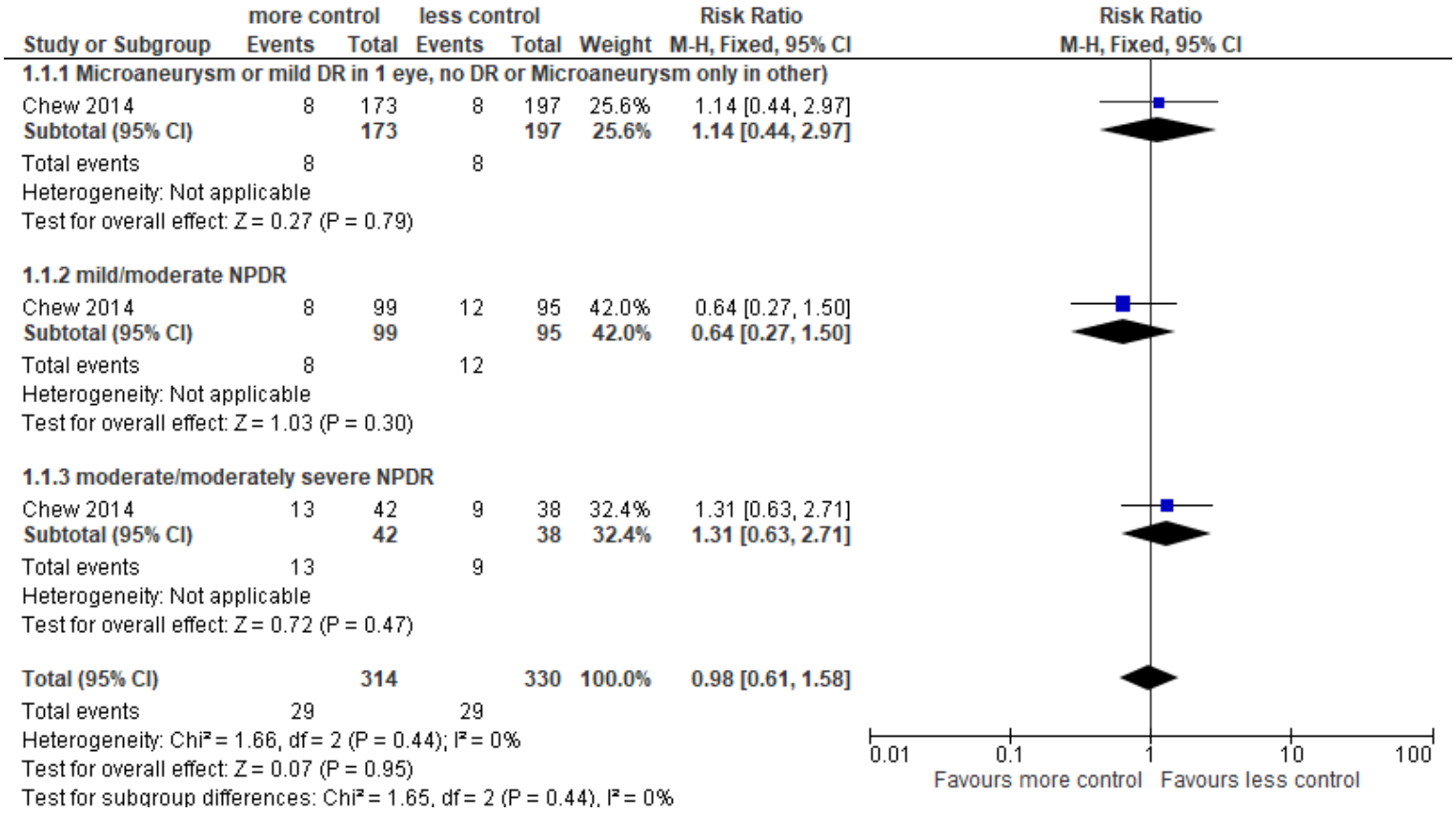


Figure 5: Four-Year Rates of Diabetic Retinopathy Severity Progression



E.2 Statins

Statins vs Placebo

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

Study or Subgroup	Statins Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gupta 2004	5	15	3	15	85.7%	1.67 [0.48, 5.76]
Sen 2002	1	25	0	25	14.3%	3.00 [0.13, 70.30]
Total (95% CI)		**40**		**40**	**100.0%**	**1.86 [0.58, 5.91]**
Total events	6		3			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)

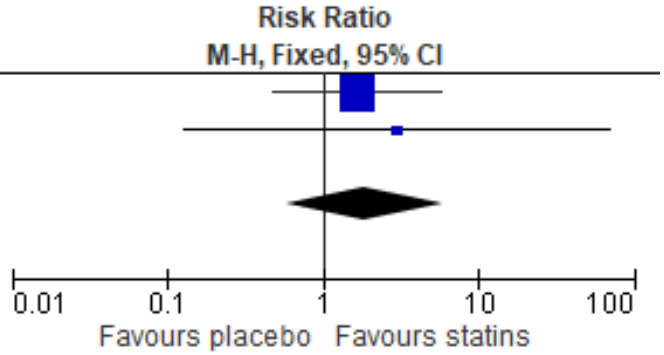


Figure 7: Status of Visual Acuity at 18-Week Follow-up (Worsened by at least two lines)

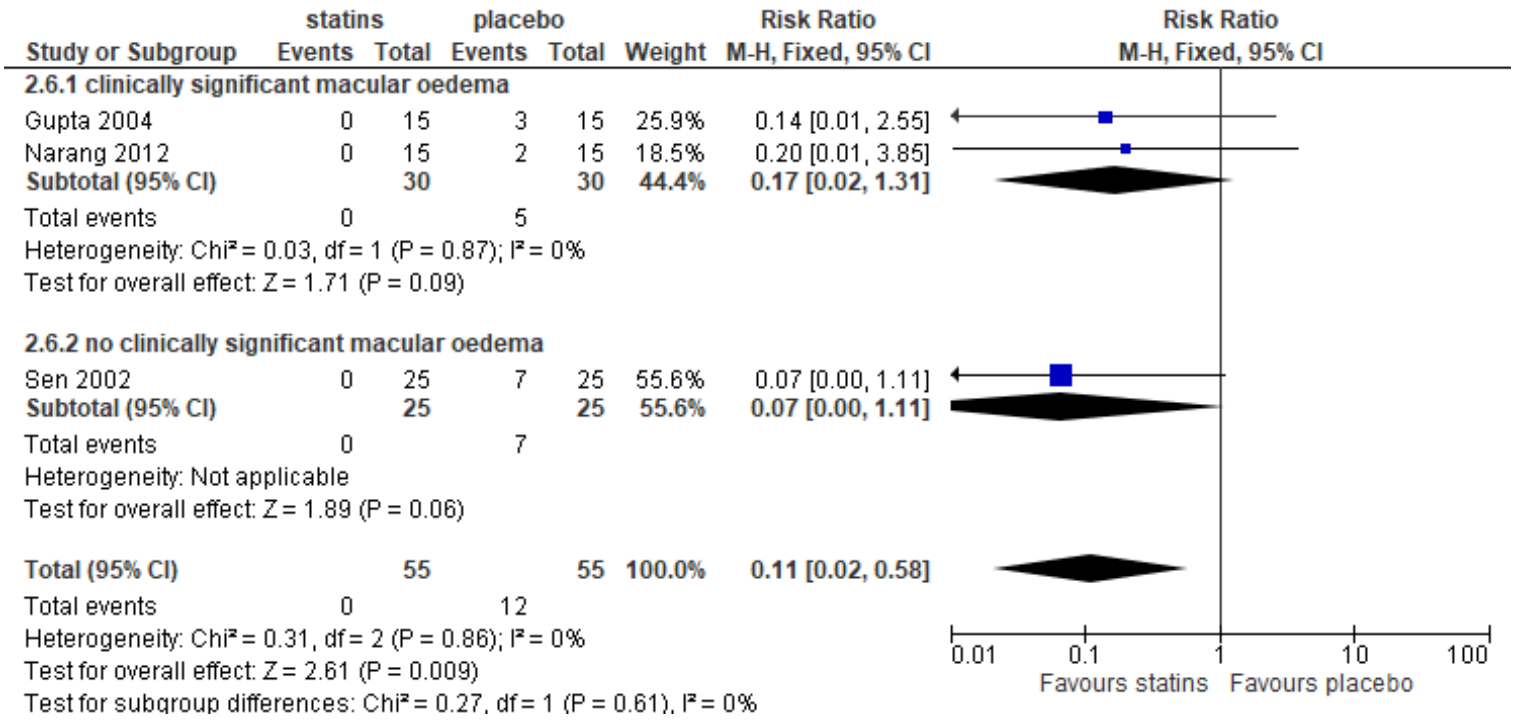


Figure 8: Macular oedema regression

Study or Subgroup	Statins Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gupta 2004	9	15	5	15	48.7%	1.80 [0.79, 4.11]
Narang 2012	6	15	8	15	51.3%	0.75 [0.34, 1.64]
Total (95% CI)		**30**		**30**	**100.0%**	**1.15 [0.49, 2.71]**
Total events	15		13			

Heterogeneity: Tau² = 0.22; Chi² = 2.28, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.32 (P = 0.75)

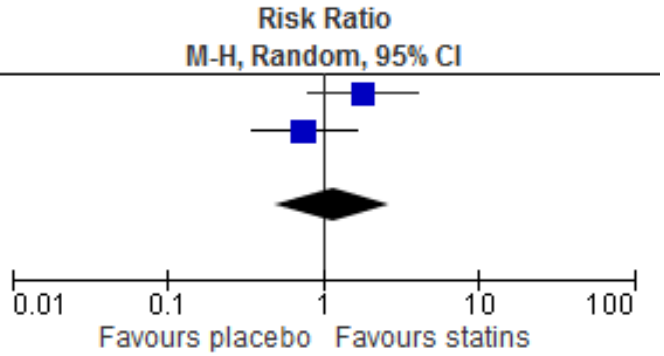
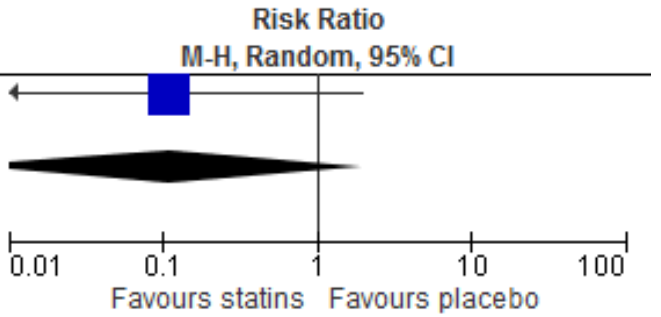


Figure 9: Development of clinically significant macular oedema at 90 days

Study or Subgroup	Statins Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sen 2002	0	25	4	25	100.0%	0.11 [0.01, 1.96]
Total (95% CI)		**25**		**25**	**100.0%**	**0.11 [0.01, 1.96]**
Total events	0		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



Intensive statin therapy vs standard statin therapy

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

Study or Subgroup	standard statin therapy Events	Total	Intensive statin therapy Events	Total	Risk Ratio M-H, Random, 95% CI
Murakami 2020	8	61	9	67	0.98 [0.40, 2.37]

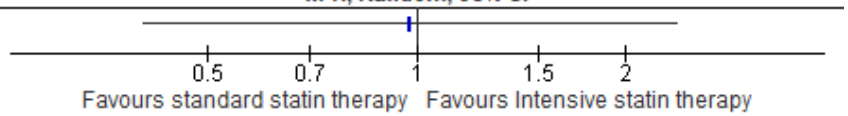
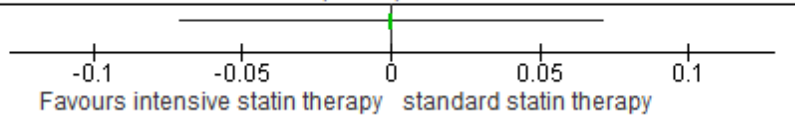


Figure 11: Changes in logMAR VA from baseline to last observation (Best-corrected decimal VA)

Study or Subgroup	intensive statin therapy Mean	SD	Total	standard statin therapy Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Murakami 2020	0	0.2364	85	0	0.2155	72	0.00 [-0.07, 0.07]



E.3Fibrates

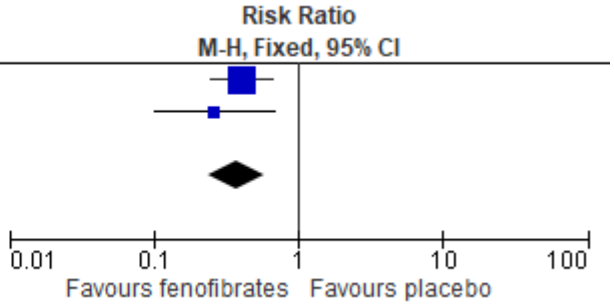
Fenofibrate vs placebo

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).

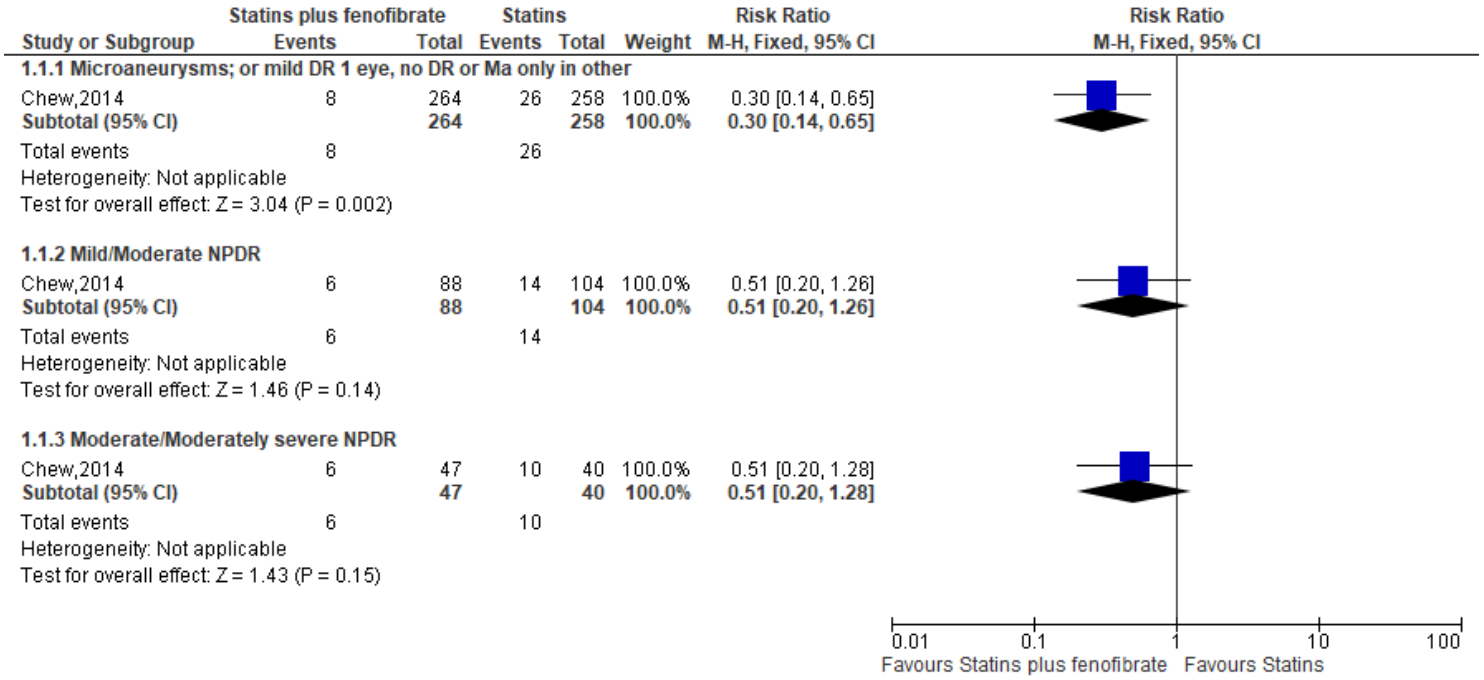
	fenofibrate		placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
ACCORD EYE study	20	399	50	402	77.3%	0.40 [0.24, 0.66]
FIELD Ophthalmology substudy	4	24	14	22	22.7%	0.26 [0.10, 0.68]
Total (95% CI)		**423**		**424**	**100.0%**	**0.37 [0.24, 0.58]**
Total events	24		64			

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 4.40 (P < 0.0001)



Statins plus fenofibrate vs Statins

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



Appendix F GRADE tables

F.1 Blood pressure control interventions

Table 18: 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	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	181 per 1000	4 more per 1000 (14 fewer to 22 more)	Risk Ratio: 1.02 [0.92, 1.12]	serious[1]	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	186 per 1000	2 fewer per 1000 (19 fewer to 17 more)	Risk Ratio: 0.99 [0.89, 1.11]	serious[1]	Not serious	Not serious	Moderate
1	RCT	273	370 per 1000	141 fewer per 1000 (211 fewer to 33 fewer)	Risk Ratio: 0.62 [0.43, 0.91]	serious[1]	NA	Not serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias

Table 19: 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	151 per 1000	8 more per 1000 (15 fewer to 32 more)	Risk Ratio 1.05 [0.90, 1.21]	Not serious	Not serious	Not serious	High

Table 20 : 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	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	500 per 1000	200 fewer per 1000 (285 fewer to 75 fewer)	Risk Ratio 0.60 [0.43, 0.85]	Not serious	NA	Not serious	High

Table 21: Four-Year Rates of Diabetic Retinopathy Severity Progression. Progression: Defined as 3 steps of progression along the ETDRS diabetic 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 less control	Risk with More control					
Overall (RR<1 favours more blood pressure control)									
Normotensive at baseline (pooled result)									
1	RCT	644	88 per 1000	2 fewer per 1000 (34 fewer to 51 more)	Risk Ratio 0.98 [0.61, 1.58]	serious[1]	NA	serious[2]	Low
Microaneurysm or mild DR in 1 eye, no DR or Ma only in other)									
1	RCT	370	41 per 1000	6 more per 1000 (23 fewer to 77 more)	Risk Ratio: 1.14 [0.44, 2.97]	serious[1]	NA	serious[2]	Low
mild/moderate NPDR (Normotensive at baseline)									
1	RCT	194	126 per 1000	45 fewer per 1000 (92 fewer to 63 more)	Risk Ratio:0.64 [0.27, 1.50]	serious[1]	NA	serious[2]	Low
moderate/moderately severe NPDR									
1	RCT	80	237 per 1000	73 more per 1000 (88 fewer to 405 more)	Risk Ratio: 1.31 [0.63, 2.71]	serious[1]	no serious	serious[2]	Low

1 >33% of weighted data from studies at moderate or high risk of bias
2 Study partially applicable to the review

F.2 Statins

Statins compared to Placebo

Table 22: Statins compared to Placebo for diabetic retinopathy. Status of Visual Acuity at 18-Week Follow-up (Improved by at least two 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	75 per 1000	65 more Per 1000 (31 fewer to 368 more)	Risk Ratio 1.86 [0.58, 5.91]	serious[1]	Not serious	Not serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias

Table 23: 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. 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.

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	218 per 1000	194 fewer Per 1000 (214 fewer to 92 fewer)	Risk Ratio: 0.11 [0.02, 0.58]	serious[1]	Not serious	Not serious	Moderate
Clinically significant macular oedema (RR<1 favours statins)									
2	RCT	60	167 per 1000	139 fewer Per 1000 (164 fewer to 52 more)	Risk Ratio: 0.17 [0.02, 1.31]	serious[1]	Not serious	Not serious	Moderate
No clinically significant macular oedema (RR<1 favours statins)									
1	RCT	50	280 per 1000	260 fewer Per 1000 (280 fewer to 31 more)	Risk Ratio: 0.07 [0.00, 1.11]	serious[1]	NA	Not serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias

Table 24: 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	433 per 1000	65 more Per 1000 (221 fewer to 740 more)	Risk Ratio: 1.15 [0.49, 2.71]	serious[1]	serious[2]	Not serious	Low

1 >33% of weighted data from studies at moderate or high risk of bias

2 I^2 >33%

Table 25: 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					
Development of CSME at 90 days (RR<1 favours statins)									
1	RCT	50	160 per 1000	142 fewer Per 1000 (158 fewer to 154 more)	Risk Ratio: 0.11 [0.01, 1.96]	serious[1]	NA	Not serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias

Intensive statin therapy vs standard statin therapy

Table 26: (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	132 per 1000	3 fewer Per 1000 (79 fewer to 181 more)	Risk Ratio: 0.98 [0.40, 2.37]	serious[1]	NA	serious[2]	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

Table 27: 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[1]	NA	serious[2]	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias
2 Mixed population with 50% population with proliferative disease

F.3 Fibrates

Fenofibrate compared to placebo for diabetic retinopathy.

Table 28: 2-step progression of retinopathy progression of diabetic retinopathy: 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).

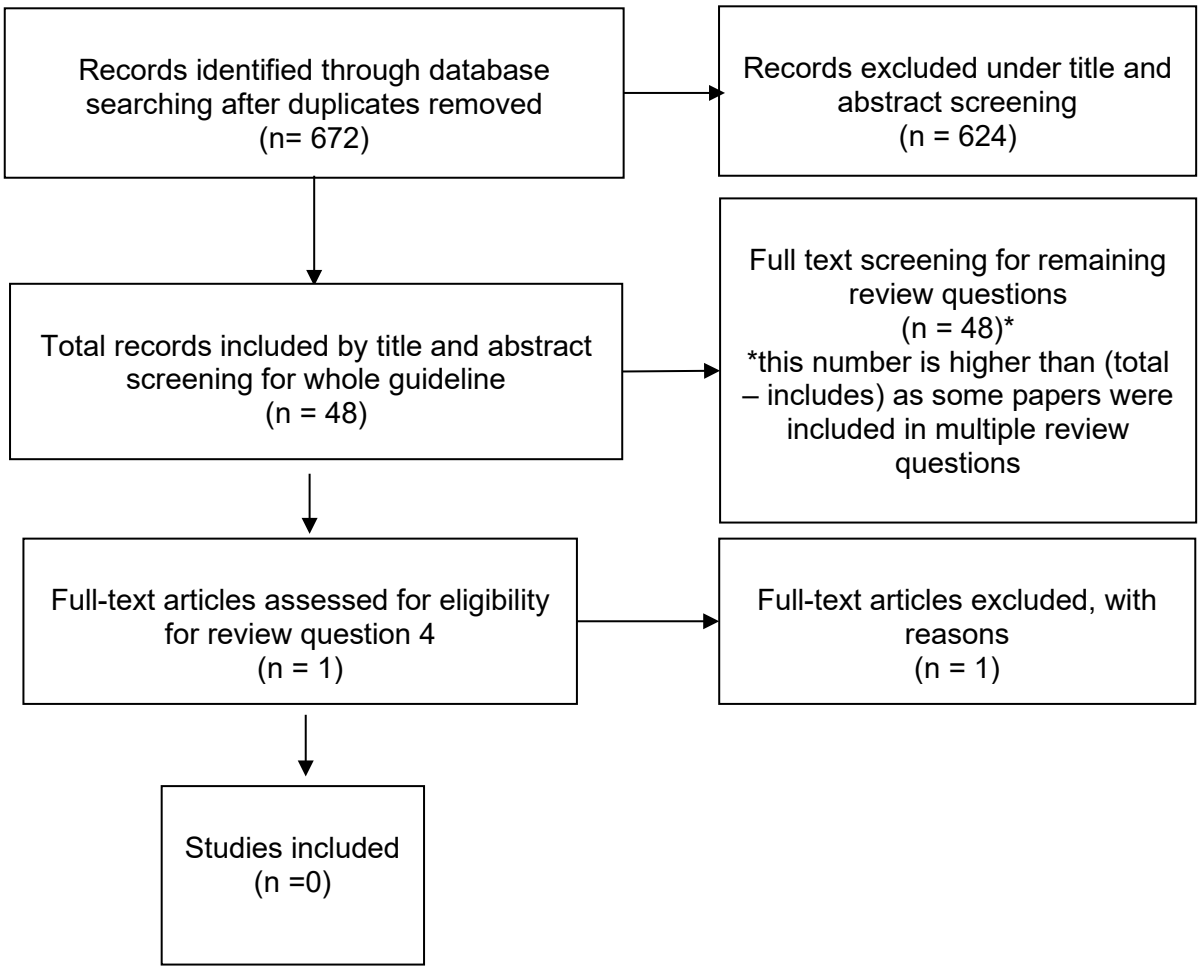
No. of studies	Study design	Sample size	Anticipated absolute effects		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Statins plus fenofibrate	Risk with Statin					
Progression of diabetic retinopathy (RR<1 favours fibrates)									
2 (FIELD study, ACCORD EYE study)	RCT	847	151 per 1000	95 fewer Per 1000 (115 fewer to 63 fewer)	Risk Ratio: 0.37 (0.24 to 0.58)	serious[1]	No serious[2]	serious[3]	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^2 < 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.

Table 29: Statins plus fenofibrate vs Statin. Four-Year Rates of Diabetic Retinopathy Severity Progression

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	101 per 1000	71 fewer Per 1000 (87 fewer to 35 fewer)	Risk Ratio: 0.30 [0.14, 0.65]	serious[1]	NA	serious[2]	Low
Mild/moderate NPDR (RR<1 favours fibrates)									
1	RCT	192	135 per 1000	66 fewer Per 1000 (108 fewer to 35 more)	Risk Ratio:0.51 [0.20, 1.26]	serious[1]	NA	serious[2]	Low
Moderate/moderately severe NPDR (RR<1 favours fibrates)									
1	RCT	87	250 per 1000	122 fewer Per 1000 (200 fewer to 70 more)	Risk Ratio: 0.51 [0.20, 1.28]	serious[1]	NA	serious[2]	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)									

Appendix G Economic evidence study selection



Appendix H – Economic evidence tables

There are no included studies in this review question.

Appendix I – Health economic model

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

Appendix J – Excluded studies

Clinical studies

Table 30: 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, design, and methods of the Action to Control	Duplicate reference

Title	Reason for exclusion
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. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2018/08/015308	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. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/07/026588	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. https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT201709207466N5	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. https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000003486	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 Safety of Rosuvastatin/Ezetimibe Combination Therapy	Does not contain a population of people with DR or DMO

Title	Reason for exclusion
and Rosuvastatin Monotherapy on Lipoprotein in Patients With Type 2 Diabetes: Multicenter Randomized Controlled Study. Diabetes Therapy 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. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 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. Archives of Iranian Medicine 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. Primary care diabetes 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. Evidence-Based Medicine 16(2): 45-46	secondary publication of a ACCORD study
Misra, A; Vikram, N K; Kumar, A (2004) Diabetic maculopathy and lipid-lowering therapy. Eye (London, England) 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. Diabetology and Metabolic Syndrome 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. Trials 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. American academy of ophthalmology: 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 ACCORD Eye Study). https://clinicaltrials.gov/show/NCT00542178	Full text paper not available
NCT04885153 (2021) Effects of Oral Fenofibrate on Retinal Thickness and	Full text paper not available

Title	Reason for exclusion
Macular Volume. https://clinicaltrials.gov/show/NCT04885153	
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. Circulation 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. The British journal of ophthalmology 91(1): 69-73	Study does not contain a relevant intervention
Panagiotoglou, TD, Ganotakis, ES, Kymionis, GD et al. (2010) Atorvastatin for diabetic macular edema in patients with diabetes mellitus and elevated serum cholesterol. Ophthalmic surgery, lasers & imaging 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. European journal of preventive cardiology	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. Journal of the Association of Physicians of India	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. Australian family physician 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]. British Medical Journal 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. Circulation 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 therapy. Vascular Health and Risk Management 13: 29-41	Study does not contain a relevant intervention
Ueshima, Kenji, Itoh, Hiroshi, Kanazawa, Nobuaki et al. (2016) Rationale and Design of the Standard Versus Intensive Statin Therapy	Study does not report outcomes in protocol

Title	Reason for exclusion
for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study: a Randomized Controlled Trial. Journal of atherosclerosis and thrombosis 23(8): 976-90	
Zhao, Y., Yu, X., Lou, Y. et al. (2020) Therapeutic Effect of Abelmoschus manihot on Type 2 Diabetic Nonproliferative Retinopathy and the Involvement of VEGF. Evidence-based Complementary and Alternative Medicine 2020: 5204917	Study does not contain a relevant intervention

Table 31: Fenofibrates studies excluded by the Cochrane review

Title	Reason for exclusion
Bonora, Bm; Albiero, M; Morieri, Ml; 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. Diabetologia 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]. International Eye Science 2018;18(12):2155-2159. [DOI: http://dx.doi.org/10.3980/j.issn.1672-5123.2018.12.08	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). https://anzctr.org.au/Trial/Registration/TrialReview.aspx?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. Ophthalmic epidemiology 2014;21(5):307-317. [DOI:10.3109/09286586.2014.949783] 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]	Patient population does not meet inclusion criteria
Matthews, Dr. Fenofibrate and statin therapy, compared with placebo and statin, slows the development of retinopathy in type 2 diabetes	Patient population does not meet inclusion criteria

Title	Reason for exclusion
patients of 10 years duration: the ACCORD study. Evidence-based medicine 2011;16(2):45-46. [DOI: 10.1136/ebm1155]	
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

Table 32: Blood pressure control studies included in the Cochrane review (Do et al. 2023) but excluded from this review.

Title	Reason for exclusion
ABCD (1) Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressiveblood pressure control in normotensive type 2 diabetic patientson albuminuria, retinopathy and strokes. Kidney International2002;61(3):1086-97	People with diabetes only, no retinopathy at baseline
ABCD (2) Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of bloodpressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care2000;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 intensiveblood pressure control with valsartan on urinary albuminexcretion 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 TrialResearch Group. Adolescent type 1 diabetes cardio-renal intervention trial (AdDIT). BMC Pediatrics 2009;9(1):79.	People with diabetes only, no retinopathy at baseline
ADDITION-Europe Griffin SJ, Borch-Johnson K, Davies MJ, Khunti K, Rutten GEHM,Sandbaek A, et al. Effect of early intensive multifactorial therapyon 5-year cardiovascular outcomes in individuals with type 2diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011;9(378):156-67. [DOI: 10.1016./S0140-6736(11)606-98-3	People with diabetes only, no retinopathy at baseline
BENEDICT Group. The BErgamo NEphrologic DIabetesComplications Trial (BENEDICT). Controlled Clinical Trials2003;24(4):442-61.	People with diabetes only, no retinopathy at baseline
Chase HP, Garg SK, Harris S, Hoops S, Jackson WE, Holmes DL.Angiotensin-converting enzyme	People with diabetes only, no retinopathy at baseline

Title	Reason for exclusion
inhibitor treatment for youngnormotensive diabetic subjects: a two-year trial. Annals ofOphthalmology 1993;25(8):284-9.	
DEMAND Ruggenenti P, Lauria G, Iliev IP, Fassi A, Ilieva AP, Rota S. Effectsof manidipine and delapril in hypertensive patients withtype 2 diabetes mellitus: the Delapril and Manidipine forNephroprotection in Diabetes (DEMAND) randomized clinicaltrial. Hypertension 2011;58(5):776-83	People with diabetes only, no retinopathy at baseline
DIRECT Prevent 1 {published data only} Chaturvedi N, DIRECT Programme Study Group. The DIabeticREtinopathy Candesartan Trials (DIRECT) Programme, rationaleand study design. Journal of the Renin-Angiotensin-Aldosterone System 2002;3(4):255-61	People with diabetes only, no retinopathy at baseline
EUCLID Chaturvedi N, Fuller JH, Pokras F, Rottiers R, Papazoglou N,Aiello LP, et al. Circulating plasma vascular endothelial growthfactor and microvascular complications of type 1 diabetesmellitus: the influence of ACE inhibition. Diabetes Medicine2001;18(4):288-94	People with diabetes only, no retinopathy at baseline
HINTS Bosworth H, Powers B, Olsen M, McCant F, Grubber J, Smith V,et al. Home blood pressure management and improved bloodpressure control: results from a randomized controlled trial.Archives of Internal Medicine 2011;171(13):1173-80.	People with diabetes only, no retinopathy at baseline
J-DOIT3 T, Kato M, Okazaki Y, Okahata S, Katsuyama H,et al. Design of and rationale for the Japan Diabetes OptimalIntegrated Treatment study for 3 major risk factors ofcardiovascular diseases (J-DOIT3): a multicenter, open-label, randomized, parallel-group trial. BMJ Open DiabetesResearch and Care 2016;4(1):e000123. [DOI: 10.1136/bmjdrc-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 intype 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. Protectiveeffect of captopril on the blood-retina barrier in normotensiveinsulin-dependent diabetic patients with nephropathy andbackground retinopathy. Graefe's Archive of Clinical andExperimental Ophthalmology 1990;228(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 thegap: effect of diabetes care management on glycemic	People with diabetes only, no retinopathy at baseline

Title	Reason for exclusion
controlamong low-income ethnic minority populations.. Diabetes Care2004;27(1):95-103.	
Pradhan R, Fong D, March C, Jack R, Rezapour G, Norris K, etal. Angiotensin-converting enzyme inhibition for the treatmentof moderate to severe diabetic retinopathy in normotensivetype 2 diabetic patients. A pilot study. Journal of Diabetes andIts Complications 2002;16(6):377-81.	People with diabetes only, no retinopathy at baseline
Rachmani R, Levi Z, Slavachevski I, Avin M, Ravid M. Teachingpatients to monitor their risk factors retards the progressionof vascular complications in high-risk patients with type 2diabetes mellitus—a randomized prospective study. DiabeticMedicine 2002;19(5):385-92	People with diabetes only, no retinopathy at baseline
RASS Klein R, Moss SE, Sinaiko AR, Zinman B, Gardiner R, Suissa S, etal. The relation of ambulatory blood pressure and pulse rate toretinopathy in type 1 diabetes mellitus. The Renin-AngiotensinSystem Study. Ophthalmology 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 enzymeinhibition on plasma creatinine and on proteinuria innormotensive type II diabetic patients. Annals of InternalMedicine 1993;118(8):577-81	People with diabetes only, no retinopathy at baseline
ROADMAP Haller H, Ito S, Izzo JL, Januszewica A, Katayama S, Menne J,et al for the ROADMAP Investigators. Olmesartan for thedelay or prevention of microalbuminuria in type 2 diabetes.New England Journal of Medicine 2011;364(10):907-17 [withSupplementary Appendix]. [CTG: NCT00185159	People with diabetes only, no retinopathy at baseline
Steno-2 Gaede J, Oellgaard J, Ibsen R, Gaede P, Nortoft E, Parving H-H,et al. A cost analysis of intensified vs conventional multifactorialtherapy in individuals with type 2 diabetes: a post hoc analysisof the Steno-2 study. Diabetologia 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 onnon-proliferative diabetic retinopathy. Chinese Medical Journal2012;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. Analysisof the effect of nine consecutive years' intensive managementand number of times achieving the target control on endpointevents in T2DM patients in Sanlitun Community Health ServiceCenter in Beijing. International Journal of	People with diabetes only, no retinopathy at baseline

Title	Reason for exclusion
Endocrinology2020;2020:Article ID 3646342. [DOI: 10.1155/2020/3646342]	

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

Appendix K - Research Recommendation

K.1.1 Research recommendation

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

K.1.2 Why this is important

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

K.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 a range of 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.

K.1.4 Modified PICO table

Population	People with non-proliferative diabetic retinopathy or diabetic macular oedema
Intervention	Intensive statin therapy
Comparison	Standard statin therapy

Outcomes	• Progression of retinopathy • Incidence of retinopathy • Incidence of macular ischemia • Changes in visual acuity • Vision-related quality of life • Adverse events •
Study design	RCT
Timeframe	5-10 year follow up
Subgroups	• People with hard exudates. / Without hard exudates • Type of diabetes • Pregnancy • Age • Ethnicity

K.1.5 Research recommendation

What is the effectiveness of fibrates to prevent progression of diabetic retinopathy in people from a range of ethnic backgrounds?

K.1.6Why this is important

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

K.1.7Rationale for research recommendation

Importance to 'patients' or the population	Current evidence does not distinguish outcomes for people of some 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 from a range of ethnic backgrounds.
Equality considerations	This question is designed to address an equality consideration about the lack of evidence for people of certain ethnicities.

K.1.8Modified PICO table

Population	People with non-proliferative diabetic retinopathy
Interventions	Fibrate therapy
Comparison	Placebo
Outcomes	• Progression of retinopathy • Incidence of retinopathy • Incidence of macular ischemia • Changes in Visual acuity • Vision-related quality of life • Adverse events
Study design	RCT
Timeframe	5-10 year follow up

Subgroups	• Type of diabetes • Pregnancy • Age • Ethnicity