National Institute for Health and Care Excellence

Guideline version (Draft)

Diabetic Retinopathy: management and monitoring

[C] Evidence reviews for effectiveness of intensive treatments to lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema

NICE guideline <number>

Evidence reviews underpinning recommendations 1.1.1 to 1.1.2 and research recommendations in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by Guideline Development Team

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ISBN:

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1.1 Review question

What is the effect of intensive treatments to rapidly lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema?

1.1.1 Introduction

There are some concerns that intensively lowering blood glucose levels may cause progression of diabetic retinopathy. There is particular concern about the potential for 'early worsening', where retinopathy may progress, and vision may worsen in the short-term after the start of intensive treatment. The aim of this review was to assess evidence in this area to inform recommendations on any monitoring that is needed when glucose lowering medicines are used. The effects of intensive blood glucose lowering treatments were assessed in comparison to fewer intensive treatments to determine the impact of intensive lowering of blood glucose on progression of diabetic retinopathy and other important outcomes such as visual acuity. This will provide an understanding of how much of an impact this treatment strategy can have on diabetic retinopathy and macular oedema.

This evidence reviews informed recommendations in the NICE guideline on the management and treatment of diabetic retinopathy, which is a new NICE guideline in this area.

1.1.2 Summary of the protocol

Table 1: Effect of intensive treatments to lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema

Population	People with non-proliferative diabetic retinopathy People with proliferative retinopathy People with diabetic macular oedema
Interventions	• Studies where the stated aim is to intensively lower blood glucose. For example: • Glucagon-like peptide 1 receptor agonist • Pioglitazone • Insulin pump therapy • Injected insulin • Sulfonylurea • SGLT-2 inhibitors • Very low-calorie diet • Treatment intensification to achieve lower glucose targets (for example, by increasing treatment dose)
Comparator	• Less intensive glucose lowering therapy (for example, metformin, DPP-4 inhibitor, Acarbose, diabetes control without glucose lowering medication)

Outcomes	• Diabetic retinopathy progression (defined as a two-step or greater progression from baseline on the ETDRS final scale)
	• Best corrected visual acuity,
	  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
	  ○ Per patient data will only be extracted when this data is not presented in a study.
	• Incidence of proliferative retinopathy
	• Incidence of macular oedema
	• Incidence of macular ischaemia
	• Peripheral vision, assessed using visual field measurement.
	
	Outcomes will be reported at 1-, 3- and 6-months following treatment onset and the latest time point reported by the study.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the Methods document .

1.1.3.1 Protocol deviation

Once the included studies were identified, it became apparent that many of the studies included people who had very mild diabetic retinopathy (microaneurysm only) or mixed populations with people who had no or unclear retinopathy at recruitment. These people are treated outside of hospital eye services and are therefore outside the scope of this guideline. However, given the limited evidence available, the committee decided that this information should still be considered as part of the review. These studies were therefore included, but downgraded for applicability to acknowledge the potential differences between those included in the studies and people with more severe eye disease who are treated by hospital eye services.

The protocol stated that results would be stratified by HbA1c reduction reported at 3 months to allow the impact of treatments that did result in a rapid reduction in HbA1c on diabetic retinopathy outcomes to be assessed. Due to the differences in populations and outcomes, it was difficult to pool the data in this way. However, the results were separated by drop in HbA1c at 3 months (greater than or less than 2%). Outcomes that reflected the effects of early worsening were presented separately to longer term outcomes.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A total of 2528 records were identified in the search. Following title and abstract screening,

Priority screening was used and the stopping criteria was reached after 1265 references were screened. 87 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 7 RCTs were included. 133 additional records were identified as part of the re-run searches, but no additional includes were identified. See the study selection flow chart in Appendix C for more information.

Comparisons

- Intensive Glycaemic Therapy Vs Standard Glycaemic Therapy (1 ACCORD eye study – Chew, 2014)
- Continuous Subcutaneous Insulin Infusion Vs Conventional Injection Treatment (1 Kroc Collaborative Study, 1984)
- Intensified Insulin Treatment Vs Standard Insulin Therapy (1 Reichard, 1993)
- Multiple Insulin Injection Therapy Vs Conventional Insulin Injection Therapy (1 Ohkubo, 1995)
- Intensive Insulin Treatment Vs Conventional Treatment (2, DCCT group 1995, DCCT group, 1998)
- Intensive Therapy Vs Standard Therapy (1 Emanuele, 1996)

1.1.4.2 Excluded studies

Overall, 81 studies were excluded following examination of the full text articles. See Appendix J for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Table of included studies

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Anonymous, 1995 **DCCT study** **USA & Canada**	Parallel-group RCT 9-year FU	**Inclusion criteria** • T1DM for 1-15 years • Eyes with very-mild-to-moderate non-proliferative retinopathy • Urinary albumin excretion ≤200 mg/day **Key exclusion criteria** • T1DM diagnosed <1 year or >15 years prior to enrolment. • T2DM • History of cardiovascular disease • Hypertension (BP ≥140/90 mmHg) • Hyperlipidaemia • Serum creatinine ≥1.2 mg/dL or creatinine clearance ≤100 ml/min/1.73 m2 BSA • Severe diabetic complications (e.g., greater degrees of retinopathy)	**(N = 363)** **Outcomes reported per eye (worse eye/better eye)** Intensive therapy: injections of insulin ≥3 times daily or via external pump; dosages adjusted according to self-monitoring of blood glucose QID • Only the population of those with retinopathy at baseline were included in this review • Primary cohorts were excluded from analysis	**(N = 351)** **Outcomes reported per eye (worse eye/better eye)** Conventional therapy: injections of insulin one or two times daily; self-monitoring of urine or blood glucose daily, ± daily adjustments	• Progression of Diabetic Retinopathy • Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up • Incidence of macular oedema as defined by the ETDRS. at 9-year follow-up • Incidence of clinically significant macular oedema as defined by the ETDRS. at 9-year follow-up • combines the severity levels

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Severe medical comorbidities			from both eyes for each person
Anonymous, 1998 **DCCT study** **USA & Canada**		**Same as above**			Reports short outcomes for above trial • Early worsening of retinopathy at 6 months/12-months • Clinically important early worsening at 6- and 12-month follow-up
Chew, 2014 ACCORD eye study USA and Canada	Parallel-group RCT 4-year FU	**Inclusion criteria** • 40 Years to 79 Years • People with an HDL cholesterol level of less than 55mg per decilitre; (1.4 mmol per litre) for women • For black ethnicity. Less than 50 mg per decilitre • 1.3 mmol per litre) for all other people.	**(N=1429) both eyes for each person** The intensive treatment arm aimed to achieve and maintain glycated haemoglobin (HbA1c) level <6.0%.	**(N=1427) both eyes for each person** The standard treatment arm targeted an HbA1c range of 7.0% to 7.9%, with an expected median value of approximately 7.5%. HbA1c 7.5%	• Progression of Diabetic Retinopathy * 4-year rates of the primary outcome, a composite of 3 steps of progression along the ETDRS diabetic retinopathy severity scale for persons or

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		* 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. **Key exclusion criteria** • Has had laser photocoagulation for DR • Has had vitrectomy surgery for DR	HbA1c 6.4%		treatment of diabetic retinopathy with photocoagulation or vitrectomy in either eye, Combines the severity levels from both eyes for each person.
Emanuele, 1996 USA	Parallel-group RCT 2-year FU	**Inclusion criteria** • Men between the ages of 40 and 69 years, • Diabetes for 15 years or less duration • Patients on a maximum dose of sulfonylurea and/or any dose of insulin • HbA1c level greater than three standard deviations above the mean of normal, 5.05 ± 3 (0.5) = 6.55% HbA1c.	**(N = 75) Outcomes combines the severity levels from both eyes for each person.** The goal of intensive therapy was to obtain an HbA1c within two standard deviations of the mean of non-diabetic subjects (4.0-6.1%). This was obtained by a four-step management technique, with patients moving to the next step only if operational goals were not	**(N = 78) Outcomes combines the severity levels from both eyes for each person.** The goal of standard therapy was good general medical care and well-being and avoiding excessive hyperglycaemia, glycosuria, ketonuria, or hypoglycaemia. This was generally	2-year Progression of Diabetic Retinopathy

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Fasting C-peptide levels were >0.21 pmol/ml **Key exclusion criteria** • People with conditions that would have precluded intensive treatment, endpoint evaluation, or continuance into a proposed long-term study • People with severe retinopathy and other ocular diseases or conditions that precluded retinal photographs	met. The steps were as follows: step 1: evening intermediate or long-acting insulin only. step 2: evening insulin with daytime glipizide. step 3: insulin, twice a day, no glipizide; and step 4: more than two injections of insulin, no glipizide. Retinopathy was assessed at baseline	accomplished with one shot of insulin per day.	
Kroc Collaborative Study, 1984 **North America and England**	Parallel-group RCT 8, Month FU	**Inclusion criteria** • 14-16 years • Type 1 diabetes • Bodyweight less than 130 per cent of ideal • Diagnosis of diabetes before the age of 35 years • Disease for less than 30 years	**(N = 35)** **Outcomes reported per eye** Patient in the intervention arm were receiving subcutaneous depot injection of mixed short acting and long-acting insulin	**(N = 35)** **Outcomes reported per eye** patients in the conventional treatment group were administered mixed insulin once a day (9) twice a day (23) or three times a day (2)	• Rates of Diabetic Retinopathy Severity Progression • Stratified by severity of retinopathy Outcomes combines the severity levels from

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• SBP less than 145mmhq • No history of ischemic heart disease • Fewer than 3 hospital admissions for ketoacidosis in the preceding year • Not pregnant or lactating • Absence of other conditions that might affect the conduct or interpretation of trial • Patients with (low C-peptide level) • Non-proliferative retinopathy **Key exclusion criteria** • People with urinary protein excretion exceeding 1g per 24 hours • Raised levels of creatine serum			both eyes for each person.
Ohkubo, 1995	Parallel-group RCT	**Inclusion criteria**	**(N = 26) Outcomes combines the severity levels from both eyes for each person.**	**(N = 25) Outcomes combines the severity levels from both eyes for each person.**	• Six-Year rates of Diabetic Retinopathy Severity Progression

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Japan	6-Year FU	• Patients with insulin-dependent diabetes mellitus (IDDM). • Simple retinopathy • Urinary albumin excretion < 300 mg/24h • Serum creatinine level < 1.5 mg/dl • <70 years of age • no history of ketoacidosis **Key exclusion criteria** Not reported	Multiple insulin injection therapy group The MIT group was defined as the group that was administered insulin 3 or more times daily (rapid-acting insulin at each meal and intermediate-acting insulin at bedtime). HbA1c *7.1%*	Conventional insulin injection therapy group The CIT group was administered 1 or 2 daily injections of intermediate-acting insulin HbA1c *9.4%*	
Reichard, 1993 **Stockholm, Sweden**	Parallel-group RCT 7.5-year FU	**Inclusion criteria** • 18 Years to 52 Years • Patients with insulin-dependent diabetes mellitus (IDDM) • Non-proliferative retinopathy, • Normal serum creatinine level	**(N = 44) Outcomes assessed were using one eye** Intensified conventional treatment (ICT) Basal-bolus insulin treatment	**(N = 53) Outcomes assessed were using one eye** Regular treatment (RT) the goal was to reduce blood glucose levels without giving rise to	• Visual Acuity measured by a loss of two lines in one eye • Incidence of proliferative retinopathy or macular oedema

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• unsatisfactory blood glucose control **Key exclusion criteria** • Alcohol/drug abuse • Proliferative retinopathy		serious or frequent hypoglycaemic episodes. Mixed insulin 2-3 times per day	*Outcomes assessed were using one eye

Notes: Abbreviations: BCVA, best corrected visual acuity; DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; FU, follow up; HbA1c, Haemoglobin A1c test; PDR, proliferative diabetic retinopathy.

1.1.6 Summary of the effectiveness evidence

Results stratified according to the actual reductions in HbA1c reported at 3 months following treatment onset to determine the impact of rapid lowering of blood glucose on diabetic retinopathy outcomes.

Interventions with a HBa1c drop greater than 2% at 3 months
Intensified insulin treatment vs standard insulin therapy (Population with non-proliferative diabetic retinopathy)

Table 3: Visual Acuity measured by a loss of two lines in one eye.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity at 7.5-year follow-up					
Reichard, 1993	RCT	89	Risk Ratio: 0.37 [0.16, 0.85]	Moderate	Favours Intensified insulin treatment

Table 4: Incidence of proliferative retinopathy or macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of proliferative retinopathy or macular oedema at 7.5-year follow-up					
Reichard, 1993	RCT	89	Risk Ratio: 0.50 [0.29, 0.85]	Moderate	Favours Intensified insulin treatment

Multiple insulin injection therapy vs conventional insulin injection therapy (people with simple retinopathy)
Table 5: Rates of Diabetic Retinopathy Severity Progression at 6-year FU

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Diabetic Retinopathy Severity Progression at 6-year follow-up					
Ohkubo, 1995	RCT	51	Risk Ratio: 0.44 [0.18, 1.08]	Moderate	Could not distinguish between treatments

Intensive insulin therapy vs insulin standard therapy (People with minimal to moderate non proliferative retinopathy) With a Fasting C-peptide levels >0.21 pmol/ml)

Table 6: Progression of retinopathy defined as a two or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 2-year FU

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Progression of retinopathy defined as a two or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 2-year follow-up					
1 Emanuele 1996	RCT	97	Risk Ratio: 0.82 [0.46, 1.47]	Moderate	Could not distinguish between treatments

Early worsening of diabetic retinopathy outcomes

Table 7: Early worsening of retinopathy defined as a three or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 6 months follow up

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subgroup: Very mild NPDR (20/<20) at 6--months follow-up					
1 DCCT group, 1998	RCT	240	Risk Ratio: 6.43 [0.83, 49.94]	Moderate	Could not distinguish between treatments
Subgroup: Very mild NPDR (20/20) at 6-months follow-up					
1 DCCT group, 1998	RCT	212	Risk Ratio: 1.35 [0.53, 3.41]	Moderate	Could not distinguish between treatments
Subgroup: Mild NPDR (35/<35) at 6-months follow-up					
1 DCCT group, 1998	RCT	192	Risk Ratio: 1.77 [0.41, 7.70]	Moderate	Could not distinguish between treatments
Subgroup: Moderate or severe NPDR (43/<43+) at 6-months follow-up					
1 DCCT group, 1998	RCT	70	Risk Ratio: 1.43 [0.48, 4.24]	Moderate	Could not distinguish between treatments

Table 8: Clinically important early worsening of retinopathy defined as development of clinically important retinopathy; Defined as severe non-proliferative diabetic retinopathy, proliferative retinopathy or clinically significant macula oedema as defined in the ETDRS at 6 months follow up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Clinically important early worsening at 6 months follow-up					
1 DCCT group, 1995	RCT	712	Risk Ratio: 1.44 [0.52, 4.01]	Moderate	Could not distinguish between treatments
Clinically important early worsening at 12-months follow-up					
1 DCCT group, 1995	RCT	712	Risk Ratio 0.96 [0.39, 2.39]	Moderate	Could not distinguish between treatments

Table 9: Recovered from early worsening at next visit (6 and 12 month follow up)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Recovered from Clinically important early worsening at next visit (6 month follow up)					
1 DCCT group, 1995	RCT	712	Risk Ratio: 2.40 [0.47-12.31]	Moderate	Could not distinguish between treatments
Recovered from Clinically important early worsening at next visit (12 month follow up)					
1 DCCT group, 1995	RCT	712	Risk Ratio: 0.32 [0.03-3.07]	Moderate	Could not distinguish between treatments

Continuous subcutaneous insulin infusion vs conventional injection treatment
Table 10: Progression of retinopathy at 8-month FU determined according to the ETDRS.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Rates of Diabetic Retinopathy Severity Progression (overall) at 8-month follow-up					
Kroc Collaborative Study, 1984	RCT	55	Risk Ratio: 2.59 [1.19, 5.65]	Moderate	Favours conventional injection treatment
Subgroup: Mild NPDR at 8-month follow-up					
Kroc Collaborative Study, 1984	RCT	27	Risk Ratio: 2.60 [1.14, 5.93]	Moderate	Favours conventional injection treatment
Subgroup: Moderate NPDR at 8-month follow-up					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Kroc Collaborative Study, 1984	RCT	24	Risk Ratio: 2.54 [0.31, 21.06]	Moderate	Could not distinguish between treatments
Subgroup: Severe NPDR or PDR 8-month follow-up					
Kroc Collaborative Study, 1984	RCT	4	No events	Moderate	Could not distinguish between treatments

Interventions with a HBa1c drop less than 2% at 3 months.

Intensive glycaemic therapy vs Standard glycaemic therapy (Population with non-proliferative diabetic retinopathy)

Table 11: Progression of retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Rates of Diabetic Retinopathy Severity Progression (overall) at 4-year follow-up					
1 (ACCORD Eye Study, Chew, 2010)	RCT	1484	Risk Ratio: 0.63 [0.47, 0.85]	Low	Favours Intensive glycaemic therapy
Subgroup: Microaneurysm or mild DR 1 eye, no DR or microaneurysm only in other at 4-year follow-up					
1 (ACCORD Eye Study, Chew, 2010)	RCT	892	Risk Ratio: 0.33 [0.17, 0.62]	Low	Favours Intensive glycaemic therapy
Subgroup: Mild/moderate NPDR at 4-year FU					
1 (ACCORD Eye Study, Chew, 2010)	RCT	386	Risk Ratio: 0.76 [0.42, 1.36]	Low	Could not distinguish between treatments
Subgroup: Moderate/moderately severe NPDR at 4-year follow-up					
1 (ACCORD Eye Study, Chew, 2010)	RCT	167	Risk Ratio: 0.77 [0.44, 1.36]	Low	Could not distinguish between treatments
Subgroup: Severe NPDR or PDR at 4-year follow-up					
1 (ACCORD Eye Study, Chew, 2010)	RCT	39	Risk Ratio: 1.14 [0.70, 1.87]	Low	Could not distinguish between treatments

Intensive insulin treatment vs conventional treatment (people with minimal to moderate non proliferative retinopathy)

Table 12:Progression of retinopathy defined as a three or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 9 years follow up

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Rates of Diabetic Retinopathy Severity Progression (overall) at 9-year follow-up					
1 DCCT group, 1995	RCT	714	Risk Ratio: 1.02 [0.74, 1.40]	Moderate	Favours Intensive insulin treatment
Subgroup: Very mild NPDR (20/20) at 9-year follow-up					
1 DCCT group, 1995	RCT	212	Risk Ratio: 1.03 [0.64, 1.67]	Moderate	Favours Intensive insulin treatment
Subgroup: Mild NPDR (35/<35) at 9-year follow-up					
1 DCCT group, 1995	RCT	192	Risk Ratio: 1.02 [0.59, 1.76]	Moderate	Favours Intensive insulin treatment
Subgroup: Moderate or severe NPDR (43/<43+) at 9-year follow-up					
1 DCCT group, 1995	RCT	70	Risk Ratio: 0.97 [0.49, 1.90]	Moderate	Could not distinguish between treatments

Table 13:Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up					
1 DCCT group, 1995	RCT	714	Risk Ratio: 0.14 [0.01, 2.66]	Moderate	Could not distinguish between treatments

Table 14: Incidence of macular oedema and clinically significant macular oedema as defined by the ETDRS. at 9-year follow-up

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of macular oedema at 9-year follow-up					
1 DCCT group, 1995	RCT	714	Risk Ratio: 0.66 [0.51, 0.85]	Moderate	Favours Intensive insulin treatment
Incidence of clinically significant macular oedema at 9-year follow-up					
1 DCCT group, 1995	RCT	714	Risk Ratio: 0.69 [0.49, 0.98]	Moderate	Favours Intensive insulin treatment

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, 670 of the studies could confidently be excluded for this review question. Two studies were 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

No unit costs have been considered as part of this review question.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered best corrected visual acuity, progression of diabetic retinopathy and incidence of macular oedema to be important outcomes in decision making. They highlighted that the effects of intensive blood glucose lowering could be different for diabetic retinopathy and for macular oedema, and so it was important to consider the outcomes separately. The committee also wanted to consider incidence of macular ischaemia and changes in peripheral vision, but these were not reported in the literature.

The committee emphasised the importance of considering the outcomes in both the short-term and longer-term. The short-term effects relate to the phenomenon of early worsening of retinopathy that can happen in the months after intensive blood glucose lowering treatment begins and the longer-term effects reflect those that are sustained after early worsening. This will help to identify whether there are any immediate effects of intensive glucose reduction and if those effects are sustained over time.

The committee also considered changes in HbA1c to be important, as this may influence the extent of early worsening. Where possible, they reviewed evidence on changes in HbA1c within the 3 months from baseline. Analysis of HbA1c reduction based on treatments was not possible for several reasons: the impact of intensive treatments on HbA1c levels were not consistently reported at 3 months, the intensive treatments were different and therefore could not be pooled, and the baseline HbA1c in the included studies varied and the committee were concerned that people with a higher baseline HbA1c haver greater risk of early worsening than those with lower HbA1c values.

1.1.11.2 The quality of the evidence

6 RCTs, one of which had 2 papers separating the short-term and long-term outcomes were included in this review. Each of these studies included people with non-proliferative retinopathy, either as the main analysis or as part of subgroup analysis. No studies evaluated the effects of intensive glucose lowering for people with proliferative retinopathy or macular oedema.

The outcomes ranged from moderate to low quality. All studies were downgraded for indirectness as a large proportion of participants were people who had very mild diabetic retinopathy (microaneurysm only) or mixed populations with people who had no or unclear retinopathy at recruitment. 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, with the limited evidence available, this information was still useful for considering the effects of intensive blood glucose lowering on people being treated in hospital eye services. Given the different populations included in the evidence base, and other differences, such as HbA1c at baseline, results from individual studies could not be pooled. This meant that most of the outcomes were from single studies with small sample sizes. This was a particular issue for the studies that reported on the short-term data that was used to judge the effects of early worsening. The committee were concerned that some of the treatments used in the older studies are not as relevant to clinical practice. This made it difficult to make strong recommendations on these effects. Studies that reported short-term outcomes were not powered to detect these early effects, and were instead designed to evaluate the longer-term effects of intensive blood glucose lowering. This made it more difficult to determine any impact on early worsening. The committee also thought that the early worsening effects may be

greater with newer treatments, supporting the need for a research recommendation on this effect (see Appendix K).

1.1.11.3 Imprecision and clinical importance of effects.

The evidence was mostly from small trials and single study analysis. The committee discussed how, for most outcomes, these limitations resulted in a high degree of imprecision that meant it was difficult to draw conclusions on whether the effects are likely to be clinically important. This limited the conclusions that could be drawn and the number of recommendations that could be made.

1.1.11.4 Benefits and harms

For people with non-proliferative diabetic retinopathy, 2 studies showed long-term benefits of intensive blood glucose reduction treatment on retinopathy outcomes. One study (Reichard 1993) compared a basal-bolus insulin treatment to regular treatment and reported evidence of benefit for intensive therapy on visual acuity at 7.5-year follow-up measured by a loss of two lines in one eye and reduced incidence of proliferative retinopathy or macular oedema. Another study (ACCORD glycemia eye study) showed that intensive therapy slowed rates of progression of retinopathy according to the ETDRS severity scale at 4 years. However, the committee noted that the subgroup analysis of this data by severity of retinopathy showed that the benefit of intensive therapy was only evident for people with very mild non-proliferative retinopathy. In the other subgroups with moderate and severe non-proliferative retinopathy, the wide confidence intervals made it difficult to reach a conclusion on the true effect of treatment. Neither of these studies reported short term outcomes within the first 6 months of follow-up and so it was not possible to determine the effects of intensive blood glucose reduction on early worsening for this group of people.

The DCCT (1995) study also considered people who have non-proliferative diabetic retinopathy, focusing on people with type 1 diabetes. The outcomes could not distinguish between intensive or conventional treatment at 6 months. However, people who kept their blood glucose levels as close to normal as possible with intensive diabetes treatment early in their disease had less progression of retinopathy and incidence of macular oedema after 9-years, compared with people who were treated with conventional therapy. The committee thought this was important and decided to use the recommendations to highlight the importance of good long-term diabetes management in relation to a person's vision. By making people more aware of this information, they can understand that good control of their diabetes can have a positive impact on their longer-term outcomes, such as vision, that they might not otherwise be aware of. Although no studies evaluated the effects of rapid glucose lowering for people with proliferative retinopathy or macular oedema, the committee thought that the recommendations were still important for these groups and so the recommendation was made for all people who have non-proliferative or proliferative diabetic retinopathy, or diabetic macular oedema. This will ensure that all patients are aware of the long-term benefits of good diabetes management and that no one misses out on important monitoring.

Another study (Kroc, 1984) compared subcutaneous depot injection of mixed short acting and long-acting insulin with standard insulin therapy. At 8-month follow-up, the results favoured conventional treatment for diabetic retinopathy progression and there were more retinopathy complications associated with the continuous infusion group. However, at 2-year follow-up the degree of retinopathy in the two treatment groups was very similar. The committee agreed that a combination of the evidence from each of these studies indicated that in people with mild to moderate non-proliferative diabetic retinopathy, while there may be some short-term negative effects of intensive blood glucose reduction on retinopathy outcomes, these effects do not

appear to be sustained and may not cause additional long-term deterioration in non-proliferative retinopathy. Instead, there may actually be some long-term benefits of intensive blood glucose reduction.

The authors were not able to show whether people who had retinopathy at baseline, who used intensive treatment had sustained progression of retinopathy. There is therefore no evidence from this study to suggest that more gradual reduction of glycemia might be associated with less risk of early worsening.

The committee discussed how the evidence related to early worsening differed to their clinical experience. Early worsening is something that they were concerned about, and they believed that many people involved in diabetes care are not aware of, despite its potential short term impact on a person's vision and progression of retinopathy. They highlighted how it is likely that the most important risk factors for early worsening are higher HbA1c levels at screening, as any substantial reduction from these high levels could have adverse effects. The committee noted that in their clinics they regularly see people with very high HbA1c levels (>11%) and the evidence did not include these people. They were also aware that new intensive therapies not covered by the evidence in this review can cause a significant drop in HbA1c and the short-term effects of these are therefore unclear. As a result, the committee decided that it was important that caution should be taken for people before starting intensive therapies and recommended that people have a review from their ophthalmologist if they are about to be given intensive treatments which will cause an intensive reduction in HbA1c. This will allow the ophthalmologist to assess the person's current eye disease status, identify any potential issues that may put them at greater risk of the early worsening, and identify any changes once they begin treatment. The committee thought this was particularly important as there is often a lack of communication between diabetologists and ophthalmologists when it comes to starting treatment, which can impact on patient outcomes.

Given the lack of high-quality research on early worsening, the committee decided that a research recommendation was needed. This includes subgroups for people with higher and lower HbA1c at baseline to identify whether some people are more at risk of the negative effects associated with this type of treatment than others (see Appendix K).

1.1.11.5 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of intensive treatments to lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema. The committee discussed the limited evidence available for making recommendations, however based on their experience they wanted to ensure people who are likely to experience an intensive drop in HbA1c are reviewed by an ophthalmologist. Although this may lead to an additional ophthalmology appointment this is unlikely to have a large resource impact over time as this additional appointment is likely to only be for a small proportion of people and is anticipated to detect signs of early worsening which may prevent the need for more intensive future treatment of diabetic retinopathy or DMO. Overall, the committee were not concerned of any resource impact as a result of the recommendations.

1.1.11.6 Other factors the committee took into account

The committee were aware of other studies that consider early worsening but did not match the protocol criteria, such as the SUSTAIN-6 study which randomised people with type 2 diabetes and background retinopathy to receive either semaglutide (intensive therapy) or placebo. The authors showed that early worsening of retinopathy was observed in 3% of those randomised to GLP-1 agonist compared to 1.8% that received placebo treatment. However,

as the population was people with background retinopathy, they did not meet the inclusion criteria for this review. The committee could not be certain whether the effects would be the same for people with more advanced retinopathy or macular oedema. However, this study highlighted that early worsening does occur following intensive treatments for some populations. This supported the need for the research recommendation into potentially early worsening effects for people with diabetic retinopathy and macular oedema.

The committee also discussed how understanding the early worsening phenomenon may now be more important given the new technologies that people who have diabetes can use to monitor their HbA1c levels. Continuous glucose monitoring devices that allow people to monitor their HbA1c means that some people may decide to attempt to lower their blood glucose on their own, with no knowledge of the short-term risks to their vision. It is therefore important to understand more about the risks of early worsening and who is likely to be most at risk of these effects.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.2 and the research recommendation on the effects of rapid blood glucose reduction.

1.1.13 References – included studies

1.1.13.1 Effectiveness

Anonymous (1995) Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. Ophthalmology 102(4): 647-61

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

Emanuele, N, Klein, R, Abraira, C et al. (1996) Evaluations of retinopathy in the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM). A feasibility study. Diabetes care 19(12): 1375-81

Kroc Collaborative Study, Group (1984) Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. The New England journal of medicine 311(6): 365-72

Ohkubo, Y, Kishikawa, H, Araki, E et al. (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes research and clinical practice 28(2): 103-17

Reichard, P; Nilsson, B Y; Rosenqvist, U (1993) The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. The New England journal of medicine 329(5): 304-9

1.1.13.2 Economic

No economic evidence was included.

1.1.13.3 Other

Appendices

Appendix A – Review protocols

Review protocol for effect of intensive treatments to lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema

ID	Field	Content
0.	PROSPERO registration number	CRD42022354246
1.	Review title	The effect of intensive treatments to rapidly lower blood glucose levels on progression of non-proliferative diabetic retinopathy
2.	Review question	Q3: What is the effect of intensive treatments to rapidly lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema?
3.	Objective	There are some concerns that rapidly lowering blood glucose levels may cause progression of diabetic retinopathy. The aim of the review is to assess

		evidence in this area to inform possible recommendations on monitoring during changes in glucose lowering medicines. This aim will be achieved by assessing the effects of intensive blood glucose lowering treatments compared to less intensive treatments – intensive treatments are more likely to result in a large and rapid reduction in blood glucose levels. Results will be stratified according to the actual reductions in HbA1c reported at 3 months following treatment onset to determine the impact of rapid lowering of blood glucose on diabetic retinopathy outcomes.
4.	Searches	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 and observational filters 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 with non-proliferative diabetic retinopathy People with proliferative retinopathy People with diabetic macular oedema
7.	Intervention	• Studies where the stated aim is to intensively lower blood glucose . For example: o Glucagon-like peptide 1 receptor agonist o Pioglitazone o Insulin pump therapy o Injected insulin o Sulfonylurea o SGLT-2 inhibitors o Very low calorie diet o Treatment intensification to achieve lower glucose targets (for example, by increasing treatment dose) •

8.	Comparators	• Less intensive glucose lowering therapy (for example, metformin, DPP-4 inhibitor, Acarbose, diabetes control without glucose lowering medication)
9.	Types of study to be included	- Randomised controlled trials - Comparative non-randomised and observational studies with a concurrent control group where adjustment has been carried out for confounding factors using one of the methods specified in NICE TSD 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal.
10.	Other exclusion criteria	Trials that were not reported in English
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom. This review will is an evidence review to inform a new NICE guideline on the treatment and monitoring of diabetic retinopathy.
12.	Primary outcomes (critical outcomes)	• Diabetic retinopathy progression (defined as a two-step or greater progression from baseline on the ETDRS final scale) Outcomes will be reported at 1, 3 and 6 months following treatment onset and the latest time point reported by the study.

13.	Secondary outcomes (important outcomes)	• Best corrected visual acuity,
		  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
		  ○ Per patient data will only be extracted when this data is not presented in a study.
		• Incidence of proliferative retinopathy
		• Incidence of macular oedema
		• Incidence of macular ischaemia
		• Peripheral vision, assessed using visual field measurement
		
		Outcomes will be reported at 1, 3 and 6 months following treatment onset and the latest time point reported by the study.

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. This review will use of the priority screening functionality within the EPPI-reviewer software. 50% of the database will be screened. Following this point, if 5% of the database is screened without finding an include based on title and abstract

		screening, screening will be stopped, and the remaining records excluded. These stopping criteria are considered appropriate based on the experience of the team, given this topic is a well defined clinical area with clear inclusion and exclusion criteria. As additional measure, the full database will be searched if there are a very small number of included studies (<30). 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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.
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 in non-randomised and comparative observational studies will be assessed using the ROBINS-I checklist.

16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. The aim of the review is to assess the effect of rapid reductions in blood glucose on diabetic retinopathy outcomes. Rapid reduction in blood glucose is not a treatment in itself, but occurs as a result of intensive treatments to lower blood glucose. Analysis will therefore be stratified according to the HbA1c reduction reported at 3 months in the intervention arm compared with the comparator arm (see section on analysis of subgroups for details) to allow the impact of treatments that did result in a rapid reduction in HbA1c on diabetic retinopathy outcomes to be assessed, and to determine whether the degree of rapid reduction mediates the effect on primary and secondary outcomes. 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. 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 and comparative observational studies assessed with ROBINS-I 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	The aim of the review is to assess the effect of rapid reductions in blood glucose on diabetic retinopathy outcomes. Rapid reduction in blood glucose is not a treatment in itself, but occurs as a result of intensive treatments to lower blood glucose. Analysis will therefore be stratified according to the HbA1c reduction reported at 3 months in the intervention arm compared with the comparator arm (see section on analysis of subgroups for details) to allow the impact of treatments that did result in a rapid reduction in HbA1c on diabetic retinopathy

		outcomes to be assessed, and to determine whether the degree of rapid reduction mediates the effect on primary and secondary outcomes. Data will be presented separately for the following groups: • Pregnant women • Non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular oedema If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Socioeconomic status • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Severity of non-proliferative retinopathy (moderate, severe and very severe). Severity of proliferative retinopathy (low risk, high risk), Severity of diabetic macular oedema (non-centre involving, centre involving)
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	

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

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Appendix B – Literature search strategies

Search design and peer review

NICE information specialists conducted the literature searches for the evidence review. The searches were run in August 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.

Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	16 Aug 2022	Wiley	Search run on 16 August 2022
Cochrane Database of Systematic Reviews (CDSR)	16 Aug 2022	Wiley	Search run on 16 August 2022
Embase	16 Aug 2022	Ovid	1974 to 2022 August 15
Epistemonikos	16 Aug 2022	Epistemonikos	Search run on 16 August 2022
HTA	16 Aug 2022	CRD	Search run on 16 August 2022
INAHTA	16 Aug 2022	INAHTA	Search run on 16 August 2022
MEDLINE	16 Aug 2022	Ovid	1946 to August 16, 2022
MEDLINE-in-Process	16 Aug 2022	Ovid	1946 to August 15, 2022
MEDLINE ePub Ahead-of-Print	16 Aug 2022	Ovid	August 15, 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: [Insulins] this term only	32

#6 MeSH descriptor: [Insulin Infusion Systems] this term only 734
#7 MeSH descriptor: [Glucagon-Like Peptide-1 Receptor] this term only 239
#8 MeSH descriptor: [Pioglitazone] this term only 1103
#9 MeSH descriptor: [Sulfonylurea Compounds] this term only 751
#10 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only 535
#11 (Sulfonylurea*):ti,ab,kw 2634
#12 (pioglitazone* or thiazolidinedione*):ti,ab,kw 3533
#13 ((insulin* NEAR/3 (inject* or pump*))):ti,ab,kw 3567
#14 (((glp 1 or glp 1r or glp-1 or glp-1r) NEAR/4 (receptor* or protein*))):ti,ab,kw 18131
#15 ("glucagon like peptide 1" or "glucagon-like peptide 1"):ti,ab,kw 3780
#16 ((glucose* NEAR/2 (control* or lower* or decreas* or reduc*))):ti,ab,kw 11044
#17 (sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor"):ti,ab,kw 438
#18 (((Intensi* or aggressiv* or rigorous* or tight*) NEAR/3 glucose* NEAR/3 (control* or lower* or decreas* or reduc*))):ti,ab,kw 462
#19 (((Intensi* or aggressiv* or rigorous* or tight* or increas*) NEAR/3 (strateg* or therap* or treat* or process* or protocol* or dose*))):ti,ab,kw 60416
#20 MeSH descriptor: [Diet] this term only 7521
#21 MeSH descriptor: [Caloric Restriction] this term only 950
#22 ((diet* NEAR/2 (control* or lower* or decreas* or reduc* or restrict*))):ti,ab,kw 27807
#23 {OR #5-#22} 125303
#24 #4 AND #23 635

Database: Embase

1 Diabetic Retinopathy/ 46870
2 Macular Edema/ 6218
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 51865
4 1 or 2 or 3 70435
5 *Insulin/ 115692
6 insulin infusion/ 9059
7 glucagon like peptide 1 receptor/ 5258
8 Pioglitazone/ 20637
9 sulfonylurea derivative/ 10018
10 sodium glucose cotransporter 2 inhibitor/ 8880
11 sulfonylurea/ 16911
12 Sulfonylurea*.tw. 12043
13 (pioglitazone* or thiazolidinedione*).tw. 15634
14 2,4 thiazolidinedione derivative/ 14077
15 sodium glucose cotransporter 2 inhibitor/ 8880
16 (insulin* adj3 (inject* or pump*)).tw. 17742
17 ((glp 1 or glp 1r or glp-1 or glp-1r) adj4 (receptor* or protein*)).tw. 8899
18 ("glucagon like peptide 1*" or "glucagon-like peptide 1*").tw. 18556
19 (glucose* adj2 (control* or lower* or decreas* or reduc*)).tw. 72592

20 (sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor*").tw. 2762
21 ((Intensi* or aggressiv* or rigorous* or tight*) adj3 glucose* adj3 (control* or lower* or decreas* or reduc*)).tw. 2051
22 ((Intensi* or aggressiv* or rigorous* or tight* or increas*) adj3 (strateg* or therap* or treat* or process* or protocol* or dose*)).tw. 551332
23 diet restriction/ or caloric restriction/ 110629
24 (diet* adj2 (control* or lower* or decreas* or reduc* or restrict*)).tw. 78961
25 or/5-24 957753
26 4 and 25 6193
27 nonhuman/ not human/ 5032008
28 26 not 27 5678
29 limit 28 to english language 5083
30 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5272951
31 29 not 30 4165
32 Clinical study/ 160007
33 Case control study/ 191458
34 Family study/ 25670
35 Longitudinal study/ 176615
36 Retrospective study/ 1288566
37 comparative study/ 963231
38 Prospective study/ 785808
39 Randomized controlled trials/ 232026
40 38 not 39 776607
41 Cohort analysis/ 879458
42 cohort analy$.tw. 17103
43 (Cohort adj (study or studies)).tw. 406364
44 (Case control$ adj (study or studies)).tw. 160229
45 (follow up adj (study or studies)).tw. 70021
46 (observational adj (study or studies)).tw. 223421
47 (epidemiologic$ adj (study or studies)).tw. 116931
48 (cross sectional adj (study or studies)).tw. 297996
49 case series.tw. 132707
50 prospective.tw. 1016218
51 retrospective.tw. 1124283
52 or/32-37,40-51 4933254
53 random:.tw. 1820674
54 placebo:.mp. 499125
55 double-blind:.tw. 232582
56 or/53-55 2089884
57 52 or 56 6511758
58 31 and 57 1683

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:(Sulfonylurea* OR pioglitazone* OR thiazolidinedione* OR "glucagon like peptide 1*" OR "glucagon-like peptide 1*" OR sglt 2* OR gliflozin* OR "sodium glucose transporter 2 inhibitor*") OR abstract:(Sulfonylurea* OR pioglitazone* OR thiazolidinedione* OR "glucagon like peptide 1*" OR "glucagon-like peptide 1*" OR sglt 2* OR gliflozin* OR "sodium glucose transporter 2 inhibitor*")) OR (title:(Insulin AND inject* OR pump*) OR abstract:(Insulin AND inject* OR pump*)) OR (title:(glp 1 OR glp 1r OR glp-1 OR glp-1r AND receptor* OR protein*) OR abstract:(glp 1 OR glp 1r OR glp-1 OR glp-1r AND receptor* OR protein*)) OR (title:(glucose* AND control* OR lower* OR decreas* OR reduc*) OR abstract:(glucose* AND control* OR lower* OR decreas* OR reduc*)) OR (title:(Intensi* OR aggressiv* OR rigorous* OR tight* AND glucose* AND control* OR lower* OR decreas* OR reduc*) OR abstract:(Intensi* OR aggressiv* OR rigorous* OR tight* AND glucose* AND control* OR lower* OR decreas* OR reduc*)) OR (title:(Intensi* OR aggressiv* OR rigorous* OR tight* OR increas* AND strateg* OR therap* OR treat* OR process* OR protocol* OR dose*) OR abstract:(Intensi* OR aggressiv* OR rigorous* OR tight* OR increas* AND strateg* OR therap* OR treat* OR process* OR protocol* OR dose*)) OR (title:(diet* AND control* OR lower* OR decreas* OR reduc* OR restrict*) OR abstract:(diet* AND control* OR lower* OR decreas* OR reduc* OR restrict*))

Database: Health Technology Assessment (HTA)

1	MeSH DESCRIPTOR Diabetic Retinopathy IN HTA	29
2	MeSH DESCRIPTOR Macular Edema IN HTA	25
3	((diabet* adj6 (retin* or eye* or macular* or maculopath*)))	225
4	#1 OR #2 OR #3	232
5	MeSH DESCRIPTOR Insulin IN HTA	82
6	MeSH DESCRIPTOR Insulin Infusion Systems IN HTA	35
7	MeSH DESCRIPTOR Glucagon-Like Peptide-1 Receptor IN HTA	1
8	MeSH DESCRIPTOR Pioglitazone IN HTA	0

9	MeSH DESCRIPTOR Sulfonylurea Compounds IN HTA	3
10	MeSH DESCRIPTOR Sodium-Glucose Transporter 2 Inhibitors IN HTA	0
11	(Sulfonylurea*)	109
12	(pioglitazone* or thiazolidinedione*)	168
13	((insulin* adj3 (inject* or pump*)))	97
14	(((glp 1 or glp 1r or glp-1 or glp-1r) adj4 (receptor* or protein*)))	12
15	(("glucagon like peptide 1*" or "glucagon-like peptide 1*"))	83
16	((glucose* adj2 (control* or lower* or decreas* or reduc*)))	202
17	((sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor*"))	2
18	(((Intensi* or aggressiv* or rigorous* or tight*) adj3 glucose* adj3 (control* or lower* or decreas* or reduc*)))	47
19	(((Intensi* or aggressiv* or rigorous* or tight* or increas*) adj3 (strateg* or therap* or treat* or process* or protocol* or dose*)))	1288
20	MeSH DESCRIPTOR Diet IN HTA	32
21	MeSH DESCRIPTOR Caloric Restriction IN HTA	2
22	((diet* adj2 (control* or lower* or decreas* or reduc* or restrict*)))	361
23	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	2192
24	#4 AND #23	31

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

#3 AND #2 70

3 (Sulfonylurea* OR pioglitazone* or thiazolidinedione* OR "glucagon like peptide 1*" OR "glucagon-like peptide 1*" OR sglt 2* OR gliflozin* OR "sodium glucose transporter 2 inhibitor*") OR (Insulin AND inject* or pump*) OR (glp 1 or glp 1r or glp-1 or glp-1r AND receptor* or protein*) OR (glucose* AND control* or lower* or decreas* or reduc*) OR (Intensi* or aggressiv* or rigorous* or tight* AND glucose* AND control* or lower* or decreas* or reduc*) OR (Intensi* or aggressiv* or rigorous* or tight* or increas* AND strateg* or therap* or treat* or process* or protocol* or dose*) OR (diet* AND control* or lower* or decreas* or reduc* or restrict*)

2 (Diabetic Retinopathy)[mh] OR (Macular Edema)[mh] OR ((diabet* AND (retin* or eye* or macular* or maculopath*)))

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28280
2 Macular Edema/ 8493
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 32680
4 1 or 2 or 3 42920
5 *Insulin/ 93633
6 Insulin Infusion Systems/ 6220
7 Glucagon-Like Peptide-1 Receptor/ 4269
8 Pioglitazone/ 4096
9 Sulfonylurea Compounds/ 6553
10 Sodium-Glucose Transporter 2 Inhibitors/ 4735
11 Sulfonylurea*.tw. 7549
12 (pioglitazone* or thiazolidinedione*).tw. 9392
13 (insulin* adj3 (inject* or pump*)).tw. 9586
14 ((glp 1 or glp 1r or glp-1 or glp-1r) adj4 (receptor* or protein*)).tw. 4719
15 ("glucagon like peptide 1*" or "glucagon-like peptide 1*").tw. 11814
16 (glucose* adj2 (control* or lower* or decreas* or reduc*)).tw. 44899
17 (sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor*").tw. 1213
18 ((Intensi* or aggressiv* or rigorous* or tight*) adj3 glucose* adj3 (control* or lower* or decreas* or reduc*)).tw. 1257
19 ((Intensi* or aggressiv* or rigorous* or tight* or increas*) adj3 (strateg* or therap* or treat* or process* or protocol* or dose*)).tw. 339448
20 Diet/ or Caloric Restriction/ 185738
21 (diet* adj2 (control* or lower* or decreas* or reduc* or restrict*)).tw. 54283
22 or/5-21 714289
23 4 and 22 2412
24 randomized controlled trial.pt. 575011
25 randomi?ed.mp. 928229
26 placebo.mp. 218694
27 or/24-26 984348
28 23 and 27 322

29	Observational Studies as Topic/	8063
30	Observational Study/	131222
31	Epidemiologic Studies/	9153
32	exp Case-Control Studies/	1346438
33	exp Cohort Studies/	2384827
34	Cross-Sectional Studies/	437059
35	Controlled Before-After Studies/	703
36	Historically Controlled Study/	222
37	Interrupted Time Series Analysis/	1684
38	Comparative Study.pt.	1911417
39	case control$.tw.	132295
40	case series.tw.	76613
41	(cohort adj (study or studies)).tw.	244047
42	cohort analy$.tw.	9290
43	(follow up adj (study or studies)).tw.	49923
44	(observational adj (study or studies)).tw.	120655
45	longitudinal.tw.	255996
46	prospective.tw.	593352
47	retrospective.tw.	578925
48	cross sectional.tw.	382610
49	or/29-48	4957907
50	23 and 49	869
51	28 or 50	1015
52	animals/ not humans/	5004235
53	51 not 52	979
54	limit 53 to english language	896

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	*Insulin/	0
6	Insulin Infusion Systems/	0
7	Glucagon-Like Peptide-1 Receptor/	0
8	Pioglitazone/	0
9	Sulfonylurea Compounds/	0
10	Sodium-Glucose Transporter 2 Inhibitors/	0
11	Sulfonylurea*.tw.	0
12	(pioglitazone* or thiazolidinedione*).tw.	2
13	(insulin* adj3 (inject* or pump*)).tw.	1
14	((glp 1 or glp 1r or glp-1 or glp-1r) adj4 (receptor* or protein*)).tw.	3
15	("glucagon like peptide 1*" or "glucagon-like peptide 1*").tw.	8
16	(glucose* adj2 (control* or lower* or decreas* or reduc*)).tw.	19
17	(sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor*").tw.	2

18 ((Intensi* or aggressiv* or rigorous* or tight*) adj3 glucose* adj3 (control* or lower* or decreas* or reduc*)).tw. 1
19 ((Intensi* or aggressiv* or rigorous* or tight* or increas*) adj3 (strateg* or therap* or treat* or process* or protocol* or dose*)).tw. 117
20 Diet/ or Caloric Restriction/ 0
21 (diet* adj2 (control* or lower* or decreas* or reduc* or restrict*)).tw. 14
22 or/5-21 160
23 4 and 22 0
24 randomized controlled trial.pt. 0
25 randomi?ed.mp. 257
26 placebo.mp. 47
27 or/24-26 269
28 23 and 27 0
29 Observational Studies as Topic/ 0
30 Observational Study/ 0
31 Epidemiologic Studies/ 0
32 exp Case-Control Studies/ 0
33 exp Cohort Studies/ 0
34 Cross-Sectional Studies/ 0
35 Controlled Before-After Studies/ 0
36 Historically Controlled Study/ 0
37 Interrupted Time Series Analysis/ 0
38 Comparative Study.pt. 0
39 case control$.tw. 44
40 case series.tw. 27
41 (cohort adj (study or studies)).tw. 189
42 cohort analy$.tw. 4
43 (follow up adj (study or studies)).tw. 6
44 (observational adj (study or studies)).tw. 92
45 longitudinal.tw. 143
46 prospective.tw. 250
47 retrospective.tw. 325
48 cross sectional.tw. 244
49 or/29-48 1017
50 23 and 49 0
51 28 or 50 0
52 animals/ not humans/ 0
53 51 not 52 0
54 limit 53 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. 491
4 1 or 2 or 3 491
5 *Insulin/ 0
6 Insulin Infusion Systems/ 0
7 Glucagon-Like Peptide-1 Receptor/ 0
8 Pioglitazone/ 0
9 Sulfonylurea Compounds/ 0
10 Sodium-Glucose Transporter 2 Inhibitors/ 0
11 Sulfonylurea*.tw. 117
12 (pioglitazone* or thiazolidinedione*).tw. 117
13 (insulin* adj3 (inject* or pump*)).tw. 152
14 ((glp 1 or glp 1r or glp-1 or glp-1r) adj4 (receptor* or protein*)).tw. 112
15 ("glucagon like peptide 1*" or "glucagon-like peptide 1*").tw. 254
16 (glucose* adj2 (control* or lower* or decreas* or reduc*)).tw. 570
17 (sglt 2* or gliflozin* or "sodium glucose transporter 2 inhibitor*").tw. 57
18 ((Intensi* or aggressiv* or rigorous* or tight*) adj3 glucose* adj3 (control* or lower* or decreas* or reduc*)).tw. 17
19 ((Intensi* or aggressiv* or rigorous* or tight* or increas*) adj3 (strateg* or therap* or treat* or process* or protocol* or dose*)).tw. 4566
20 Diet/ or Caloric Restriction/ 0
21 (diet* adj2 (control* or lower* or decreas* or reduc* or restrict*)).tw. 611
22 or/5-21 6194
23 4 and 22 30
24 randomized controlled trial.pt. 1
25 randomi?ed.mp. 13058
26 placebo.mp. 2610
27 or/24-26 13876
28 23 and 27 6
29 Observational Studies as Topic/ 0
30 Observational Study/ 2
31 Epidemiologic Studies/ 0
32 exp Case-Control Studies/ 0
33 exp Cohort Studies/ 0
34 Cross-Sectional Studies/ 0
35 Controlled Before-After Studies/ 0
36 Historically Controlled Study/ 0
37 Interrupted Time Series Analysis/ 0
38 Comparative Study.pt. 0
39 case control$.tw. 2292
40 case series.tw. 2357
41 (cohort adj (study or studies)).tw. 8838
42 cohort analy$.tw. 302
43 (follow up adj (study or studies)).tw. 573
44 (observational adj (study or studies)).tw. 4034
45 longitudinal.tw. 6563
46 prospective.tw. 11383
47 retrospective.tw. 17723
48 cross sectional.tw. 10646
49 or/29-48 49200

50	23 and 49	6
51	28 or 50	10
52	animals/ not humans/	0
53	51 not 52	10
54	limit 53 to english language	10

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: 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

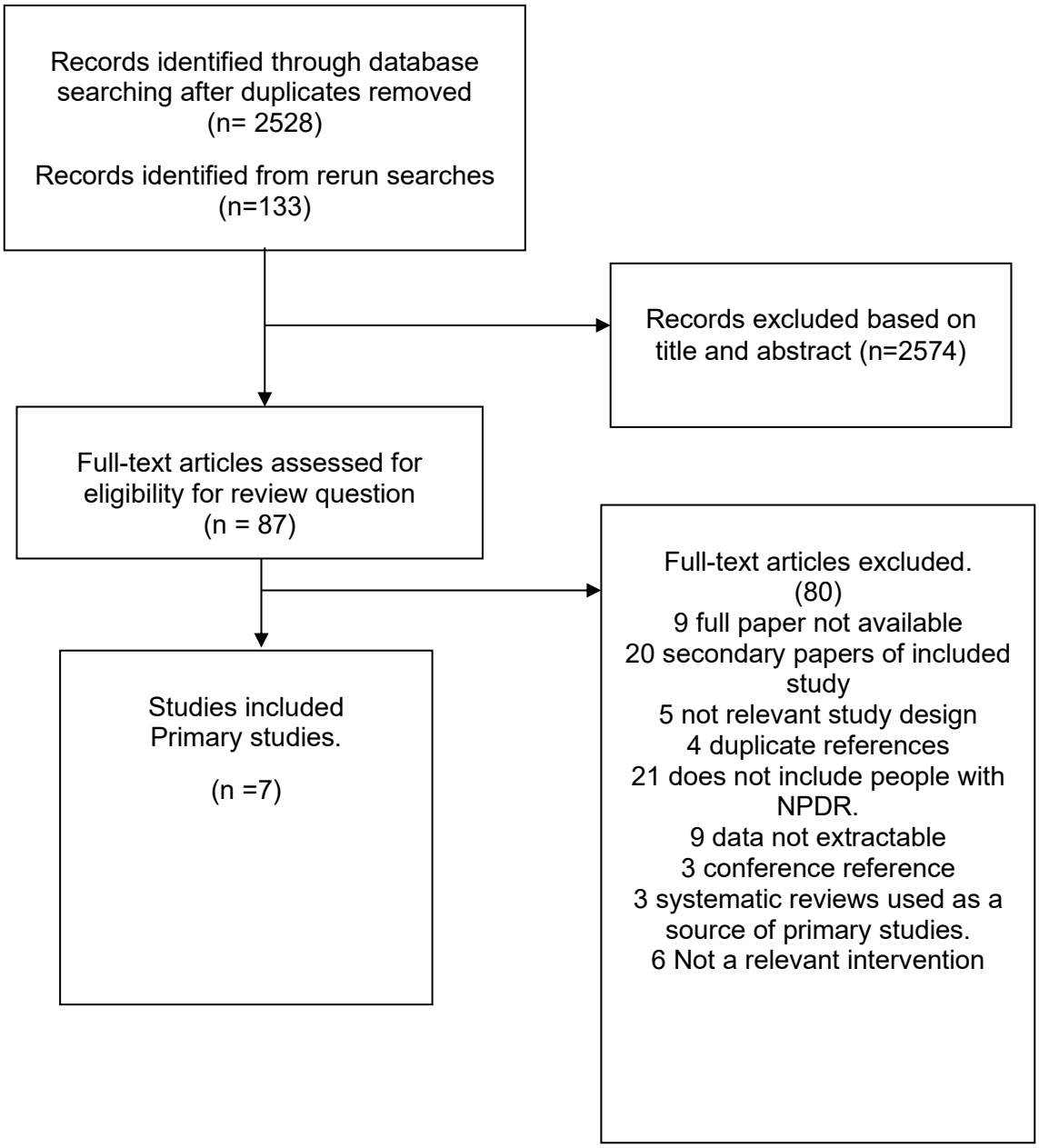
Cohort studies:

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



Appendix D – Effectiveness evidence

Anonymous, DCCT Diabetes Control and Complications Trial Research Group 1995

Bibliographic Reference	Anonymous; Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group.; Ophthalmology; 1995; vol. 102 (no. 4); 647-61

Study details

Study location	USA & Canada
Sources of funding	Supported by the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Center for Research Resources, and various sponsors.
Inclusion criteria	T1DM, as evidenced by deficient C-peptide secretion. Age: 13-39 years To be eligible for primary prevention cohort: T1DM for 1-5 years No retinopathy as detected by seven-field stereoscopic fundus photography. Urinary albumin excretion ≥40 mg/day To be eligible for secondary prevention cohort: T1DM for 1-15 years Very-mild-to-moderate non-proliferative retinopathy Urinary albumin excretion ≤200 mg/day
Exclusion criteria	T1DM diagnosed <1 year or >15 years prior to enrolment.

	T2DM History of cardiovascular disease Hypertension (BP ≥140/90 mmHg) Hyperlipidaemia Serum creatinine ≥1.2 mg/dL or creatinine clearance ≤100 ml/min/1.73 m2 BSA Severe diabetic complications (e.g., greater degrees of retinopathy) Severe medical comorbidities
Intervention(s)	**Intensive therapy:** injections of insulin ≥3 times daily or via external pump; dosages adjusted according to self-monitoring of blood glucose QID
Comparator	**Conventional therapy:** injections of insulin one or two times daily; self-monitoring of urine or blood glucose daily, ± daily adjustments
Outcome measures	Progression of Diabetic Retinopathy Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up Incidence of macular oedema as defined by the ETDRS. at 9-year follow-up Incidence of clinically significant macular oedema as defined by the ETDRS. at 9-year follow-up
Number of participants	714
Duration of follow-up	Long-term follow-up: 9-years

Study arms

Intensive Therapy (INT) (N = 363)

Conventional Group (CONV), (N = 352)

Baseline Characteristics

Section	Answer
Baseline Characteristics	
Age (yrs)	27 ± 7*
Men(%)	54

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable – population includes people with Very-mild non-proliferative retinopathy.

Anonymous, 1998

Bibliographic Reference	Anonymous; Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial.; Archives of ophthalmology (Chicago, Ill. : 1960); 1998; vol. 116 (no. 7); 874-86

Study details

Secondary publication of another included study – see primary study for details	Anonymous; Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group.; Ophthalmology; 1995; vol. 102 (no. 4); 647-61
Duration of follow-up	Short-term follow-up: 6 months and 12 months

Study arms

Intensive Therapy (INT) (N = 363)

Conventional Group (CONV), (N = 352)

Baseline Characteristics

Section	Answer
Age (yrs)	26 (8)
Men(%)	51%

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable – people with background retinopathy

Chew, 2014

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	7 Clinical Center Networks
Study dates	The ACCORD Eye study began in October 2003, participants enrolled by February 2006
Sources of funding	Funding from: 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

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. 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.
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)	The intensive treatment arm aimed to achieve and maintain glycated haemoglobin (HbA1c) level <6.0%.
Comparator	The standard treatment arm targeted an HbA1c range of 7.0% to 7.9%, with an expected median value of approximately 7.5%.
Outcome measures	Progression of Diabetic Retinopathy
Number of participants	ETDRS grading at Baseline Baseline steps 2-4: microaneurysm or mild DR 1 eye, no DR or microaneurysm only in other (N=892) Baseline steps 5-6: mild/moderate NPDR (N=386) Baseline steps 7-9: moderate/moderately severe NPDR (N=167) Baseline steps 10-17: severe NPDR or PDR (N=39)
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

Study arms

Intensive Treatment (N = 1429)

Standard Treatment (N = 1427)

Characteristics

Study-level characteristics

Characteristic	Study (N = 2856)
% Female Sample size	n = 1090; % = 38.2
Mean age (SD) Mean (SD)	61.6 (6.3)

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate
Overall bias and Directness	Overall Directness	Partially applicable *(includes a mixed population of people with and without retinopathy at baseline; only those with retinopathy ETDRS grading at baseline were included in this review)*

Emanuele, 1996

Bibliographic Reference	Emanuele, N; Klein, R; Abraira, C; Colwell, J; Comstock, J; Henderson, W G; Levin, S; Nuttall, F; Sawin, C; Silbert, C; Lee, H S; Johnson-Nagel, N; Evaluations of retinopathy in the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM). A feasibility study.; Diabetes care; 1996; vol. 19 (no. 12); 1375-81

Study details

Study location	USA
Study setting	Central Reading Center at the Department of Ophthalmology, University of Wisconsin Medical School, Madison.
Sources of funding	Not reported
Inclusion criteria	Patients were men between the ages of 40 and 69 years, Diabetes for 15 years or less duration Patients on a maximum dose of sulfonylurea and/or any dose of insulin HbA1c level greater than three standard deviations above the mean of normal, 5.05 ± 3 (0.5) = 6.55% HbA1c. Fasting C-peptide levels were >0.21 pmol/ml
Exclusion criteria	patients were excluded if they had conditions that would have precluded intensive treatment, endpoint evaluation, or continuance into a proposed long-term study patients with severe retinopathy and other ocular diseases or conditions that precluded retinal photographs
Intervention(s)	The goal of intensive therapy was to obtain an HbA1c within two standard deviations of the mean of non-diabetic subjects (4.0-6.1%). This was obtained by a four-step management technique, with patients moving to the next step only if operational goals were not met. The steps were as follows: step 1: evening intermediate or long-acting insulin only. step 2: evening insulin with daytime glipizide.

	step 3: insulin, twice a day, no glipizide; and step 4: more than two injections of insulin, no glipizide. Retinopathy was assessed at baseline
Comparator	The goal of standard therapy was good general medical care and well-being and avoiding excessive hyperglycaemia, glycosuria, ketonuria, or hypoglycaemia. This was generally accomplished with one shot of insulin per day.
Outcome measures	Progression of Diabetic Retinopathy
Number of participants	153
Duration of follow-up	12 and 24 months

Study arms

Intensive therapy (N = 75)

Standard therapy (N = 78)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 153)**

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

Section	**Question**	**Answer**
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (people with background retinopathy)

Kroc Collaborative Study, 1984

Bibliographic Reference	Kroc Collaborative Study, Group; Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial.; The New England journal of medicine; 1984; vol. 311 (no. 6); 365-72

Study details

Study location	North America and England
Study setting	6 Clinical Centres
Study dates	**Not reported**
Inclusion criteria	14-16 years Type 1 Diabetes bodyweight less than 130 per cent of ideal diagnosis of diabetes before the age of 35 years disease for less than 30 years SBP less than 145 mmHq No history of ischemic heart disease fewer than 3 hospital admissions for ketoacidosis in the preceding year Not pregnant or lactating Absence of other conditions that might affect the conduct or interpretation of trial Patients with (low C-peptide level) Non-proliferative retinopathy
Exclusion criteria	People with urinary protein excretion exceeding 1g per 24 hours

	Raised levels of creatine serum
Intervention(s)	Patient received subcutaneous depot injection of mixed short acting and long-acting insulin
Comparator	patients in the conventional treatment group were administered mixed insulin once a day (9) twice a day (23) or three times a day (2)
Number of participants	70
Duration of follow-up	8 months 2 years
Loss to follow-up	1 in the conventional treatment group and 2 in the continuous infusion group had incomplete photographic data and were excluded

Study arms

Continuous insulin infusion (N = 35)

Conventional injection treatment (N = 35)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 70)**
% Female Sample size	n = 35; % = 50

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (background and very mild retinopathy)

Ohkubo, 1995

Bibliographic Reference	Ohkubo, Y; Kishikawa, H; Araki, E; Miyata, T; Isami, S; Motoyoshi, S; Kojima, Y; Furuyoshi, N; Shichiri, M; Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.; Diabetes research and clinical practice; 1995; vol. 28 (no. 2); 103-17

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan
Sources of funding	This study was supported in part by Diabetes Mellitus Research Grants, the Ministry of Health and Welfare, Japan.
Inclusion criteria	To be included in the secondary intervention cohort, patients with insulin-dependent diabetes mellitus (IDDM). simple retinopathy urinary albumin excretion < 300 mg/24h serum creatinine level < 1.5 mg/dl <70 years of age no history of ketoacidosis

Exclusion criteria	not reported
Intervention(s)	Multiple insulin injection therapy group (MIT grow, n = 55). The MIT group was defined as the group that was administered insulin 3 or more times daily (rapid-acting insulin at each meal and intermediate-acting insulin at bedtime).
Comparator	Conventional insulin injection therapy group (CIT group, n = 55) The CIT group was administered 1 or 2 daily injections of intermediate-acting insulin
Number of participants	One hundred and ten patients were divided into 2 cohorts - the primary-prevention cohort (n = 55) and the secondary-intervention cohort (n = 55).
Duration of follow-up	6 years
Loss to follow-up	3 patients died (2 in the MIT group and 1 in the CIT group), 3 patients had moved to another city (1 in the MIT group and 2 in the CIT group), and 2 patients had changed from conventional insulin injection therapy to multiple insulin injection therapy.

Study arms

CIT group (N = 25)

MIT group (N = 26)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 51)**
% Female	n = 28
Sample size	

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (allocation concealment not clear)
Overall bias and Directness	Overall Directness	Partially applicable (people with no and background retinopathy)

Reichard, 1993

Bibliographic Reference	Reichard, P; Nilsson, B Y; Rosenqvist, U; The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus.; The New England journal of medicine; 1993; vol. 329 (no. 5); 304-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	Stockholm, Sweden
Study setting	Karolinska Institute
Study dates	1982
Sources of funding	This study was supported by grants from the Swedish division of NOVO-Nordisk Inc., Boehringer Mannheim Scand. Inc., and the Swedish Medical Research Council
Inclusion criteria	18 Years to 52 Years (Adult) patients with insulin-dependent diabetes mellitus (IDDM) non-proliferative retinopathy, normal serum creatinine levels unsatisfactory blood glucose control

Exclusion criteria	Alcohol/drug abuse Proliferative retinopathy
Intervention(s)	Basal-bolus insulin treatment
Comparator	In the RT group the goal was to reduce blood glucose levels without giving rise to serious or frequent hypoglycaemic episodes. Mixed insulin 2-3 times per day
Number of participants	102
Duration of follow-up	7.5 years
Loss to follow-up	96 patients remained in the study, while five patients had died, and one had moved to another area.

Study arms

Intensified Conventional Treatment (ICT) (N = 44)

Regular Treatment (RT) (N = 53)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 102)**
% Female	n = 47
Sample size	

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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (included people with background retinopathy)

Appendix E – Forest plots

Results stratified according to the actual reductions in HbA1c reported at 3 months following treatment onset to determine the impact of rapid lowering of blood glucose on diabetic retinopathy outcomes.

E.1.1 Interventions with a HBa1c drop greater than 2% at 3 months

E.1.1.1 Intensified Insulin Treatment Vs Standard Insulin Therapy

Figure 1: Best corrected visual acuity (Visual Acuity measured by a loss of two lines in one eye; RR less than 1 favours intensified insulin treatment)

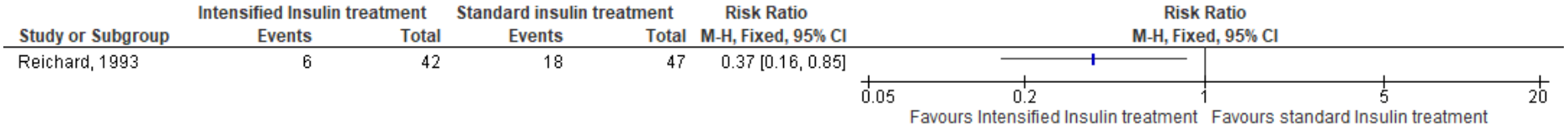
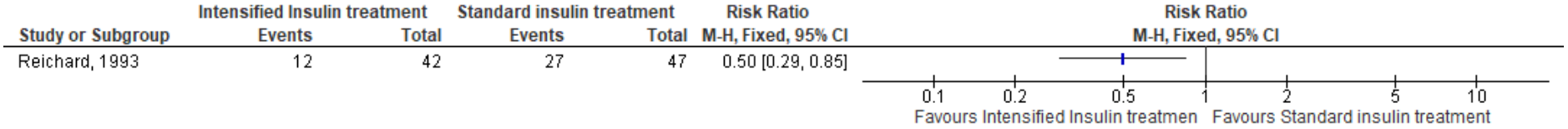
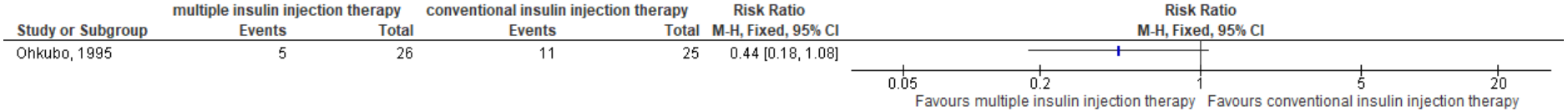


Figure 2: Incidence of proliferative retinopathy or macular oedema (RR less than 1 favours intensified insulin treatment)



E.1.1.2 Multiple insulin injection therapy vs conventional insulin injection therapy

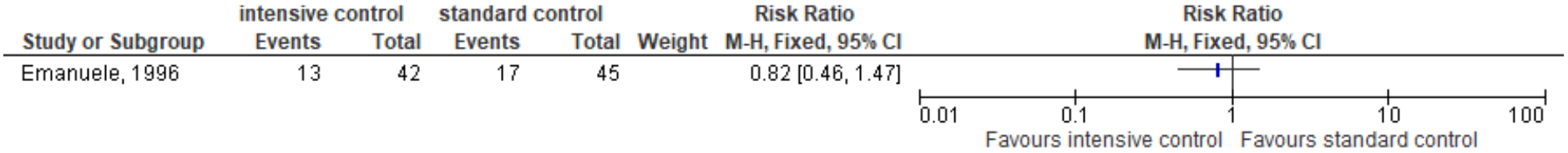
Figure 3: Six-Year Diabetic Retinopathy Severity Progression (RR less than 1 favours multiple insulin injection therapy)



E.1.1.3 Intensive insulin therapy vs insulin standard therapy

People with minimal to moderate non proliferative retinopathy with a Fasting C-peptide levels >0.21 pmol/ml

Figure 4: Progression of retinopathy defined as a two or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 2-year FU (RR less than 1 favours intensive control)

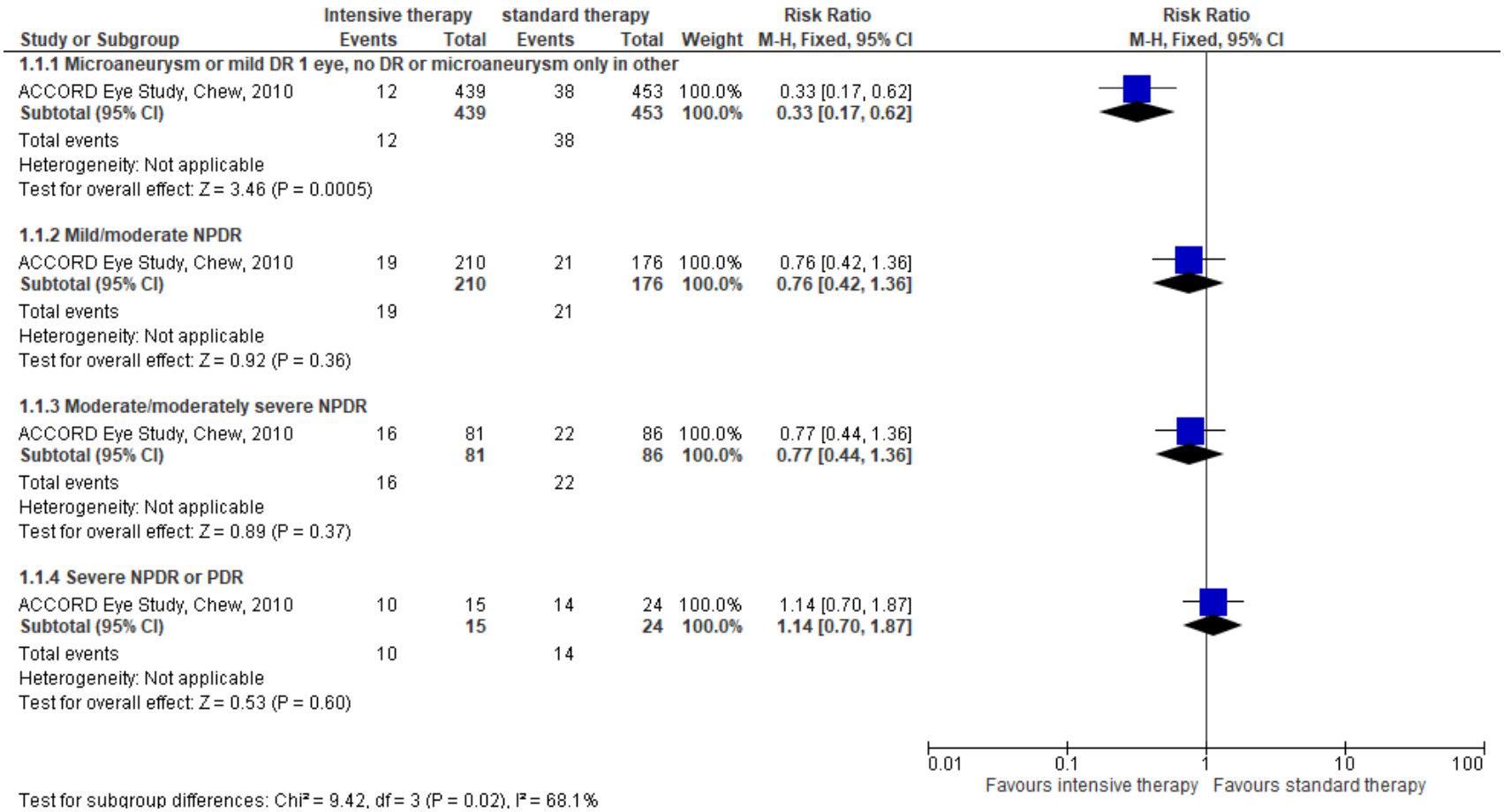


E.1.2 Interventions with a HBa1c drop less than 2% at 3 months.

E.1.2.1 Intensive glycaemic therapy vs Standard glycaemic therapy

Population with diabetic non proliferative retinopathy

Figure 5: Four-Year Rates of Diabetic Retinopathy Severity Progression (RR less than 1 favours intensive therapy)



E.1.2.1 Intensive Insulin Treatment Vs Conventional Treatment

Figure 6: 9-Year rates of Diabetic Retinopathy Severity Progression (RR less than 1 favours intensive insulin treatment)

Study or Subgroup	Intensive insulin treatment Events	Total	Conventional insulin treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.2 Very mild NPDR						
DCCT group, 1995	26	105	24	100	45.5%	1.03 [0.64, 1.67]
Subtotal (95% CI)		**105**		**100**	**45.5%**	**1.03 [0.64, 1.67]**
Total events	26		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
5.1.3 Mild NPDR						
DCCT group, 1995	18	79	23	103	37.0%	1.02 [0.59, 1.76]
Subtotal (95% CI)		**79**		**103**	**37.0%**	**1.02 [0.59, 1.76]**
Total events	18		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
5.1.4 Moderate or severe NPDR						
DCCT group, 1995	8	18	11	24	17.5%	0.97 [0.49, 1.90]
Subtotal (95% CI)		**18**		**24**	**17.5%**	**0.97 [0.49, 1.90]**
Total events	8		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**202**		**227**	**100.0%**	**1.02 [0.74, 1.40]**
Total events	52		58			
Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² = 0%						

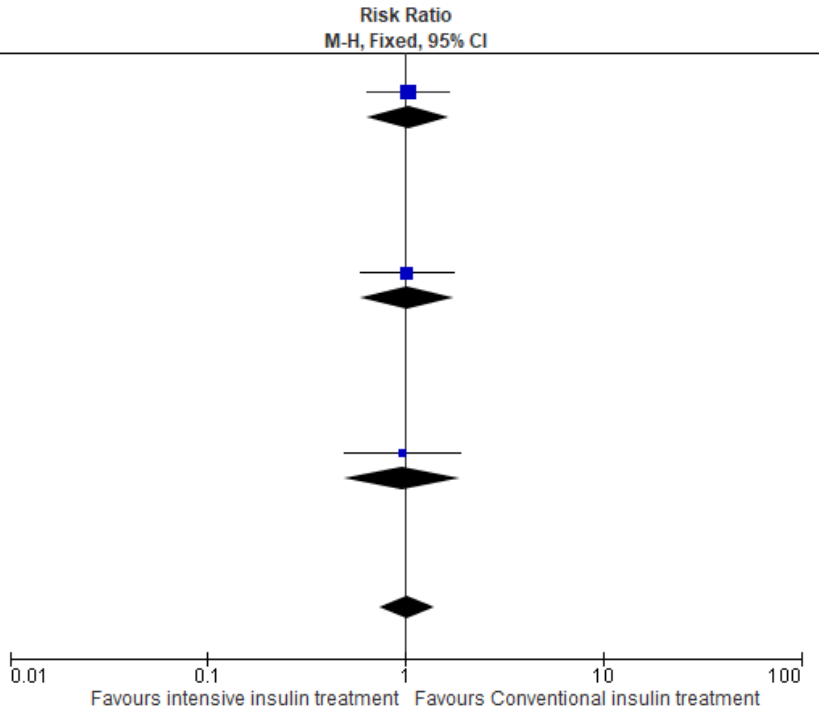


Figure 7: Loss of vision (visual acuity, 20/200 or worse) at 9-year FU (RR less than 1 favours intensive insulin treatment)

Study or Subgroup	Intensive insulin treatment Events	Total	Conventional insulin treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
DCCT group, 1995	0	363	3	351	0.14 [0.01, 2.66]

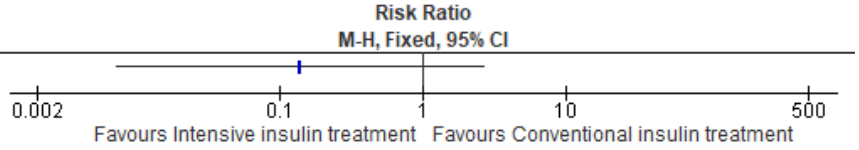


Figure 8: Incidence of macular oedema at 9-year FU (RR less than 1 favours intensive insulin treatment)

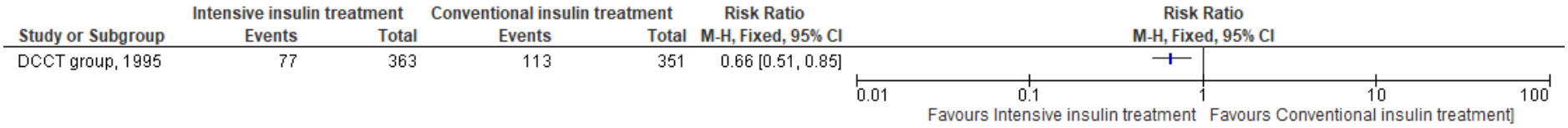
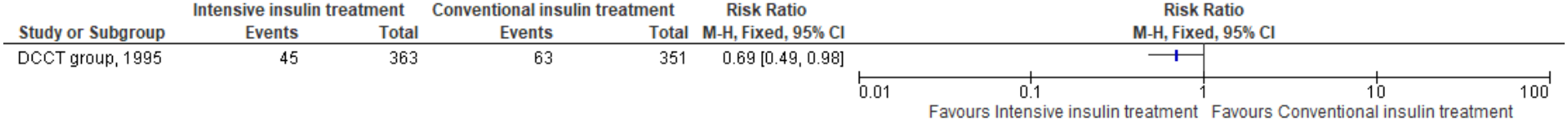


Figure 9: Incidence of clinically significant macular oedema at 9-year FU (RR less than 1 favours intensive insulin treatment)



E.1.3 Early worsening of retinopathy outcomes

E.1.3.1 Intensive Insulin Treatment Vs Conventional Treatment

Figure 10: Early worsening of retinopathy defined as a three or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 6 months follow up (RR less than 1 favours intensive treatment)

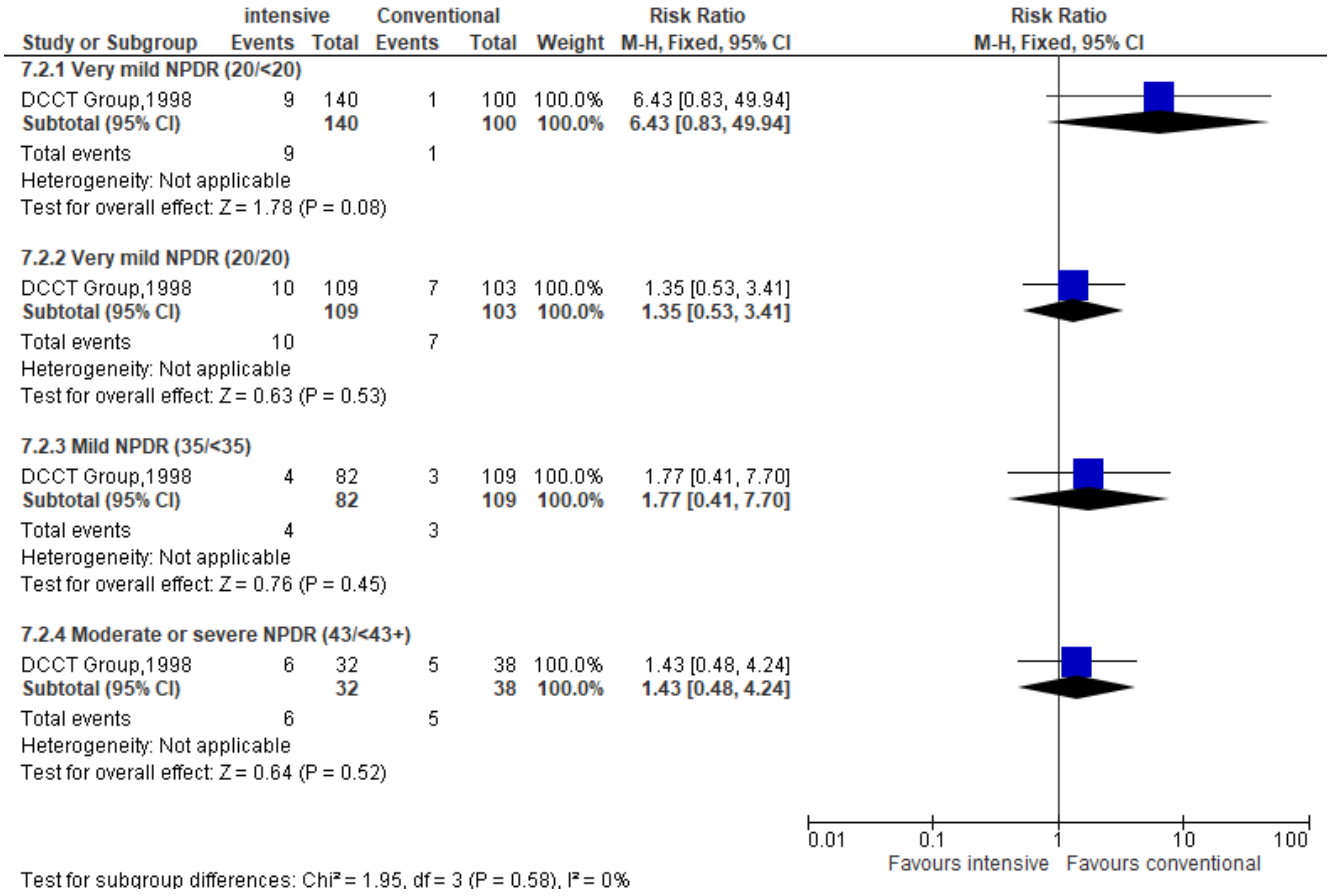


Figure 11: Clinically important early worsening of retinopathy at 6 months follow up (RR less than 1 favours intensive treatment)
Defined as development of severe non-proliferative diabetic retinopathy, proliferative retinopathy or clinically significant macula oedema as defined in the ETDRS

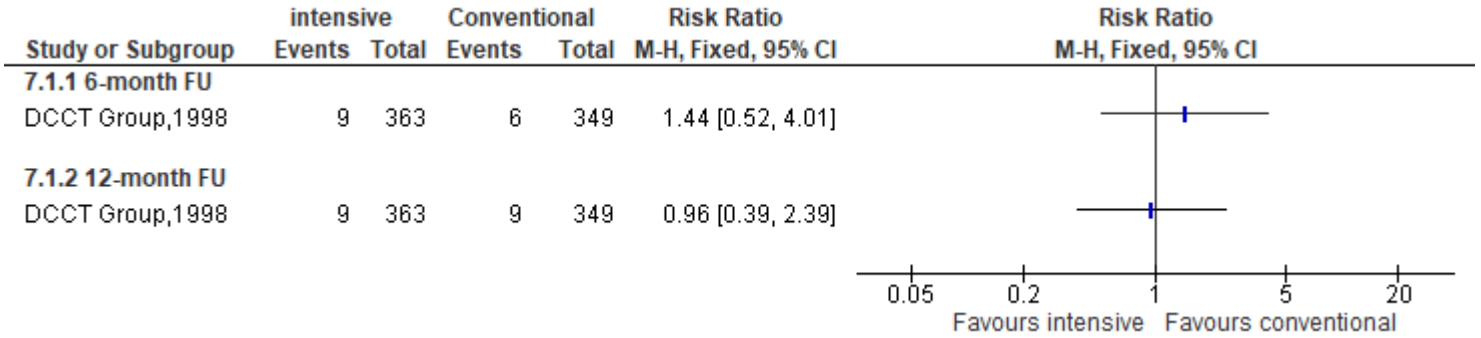
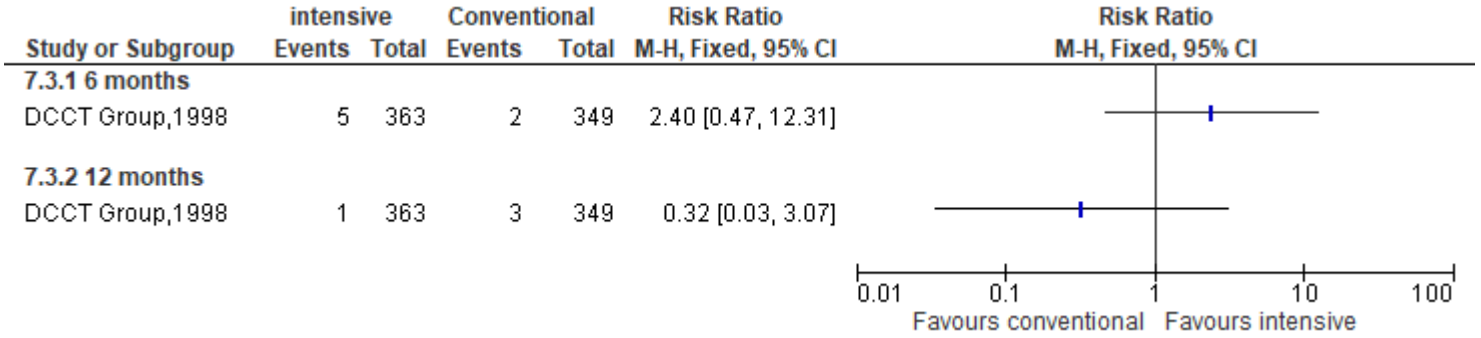


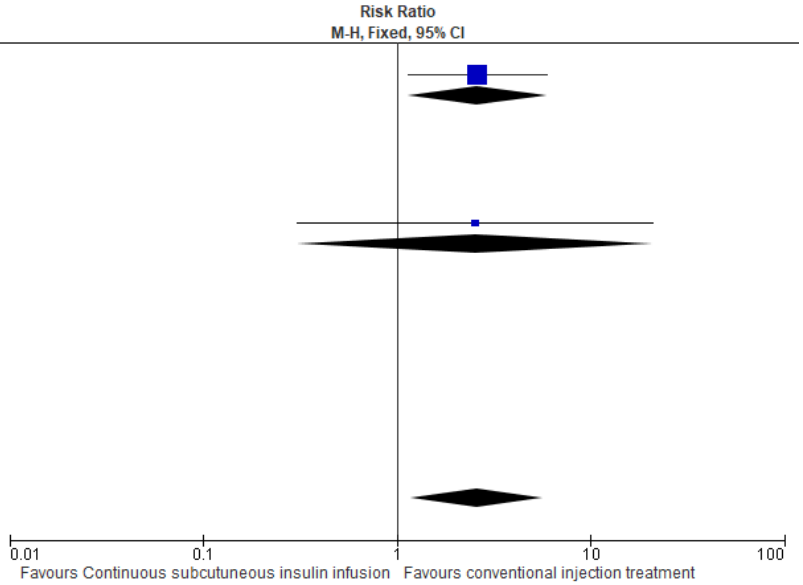
Figure 12: Recovered from early worsening at next visit (6 and 12 months follow up)



E.1.3.2 Continuous subcutaneous insulin infusion vs conventional injection treatment

Figure 13: 8 months Rates of Diabetic Retinopathy Severity Progression (RR less than 1 favours continuous subcutaneous insulin infusion)

	Continuous subcutuneous insulin infusion		conventional injection treatment			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
2.1.1 Mild NPDR						
Kroc Collaborative Study, 1984	13	15	4	12	80.4%	2.60 [1.14, 5.93]
Subtotal (95% CI)		**15**		**12**	**80.4%**	**2.60 [1.14, 5.93]**
Total events	13		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
2.1.2 Moderate NPDR						
Kroc Collaborative Study, 1984	3	13	1	11	19.6%	2.54 [0.31, 21.06]
Subtotal (95% CI)		**13**		**11**	**19.6%**	**2.54 [0.31, 21.06]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
2.1.3 Severe NPDR and PDR						
Kroc Collaborative Study, 1984	0	2	0	2		Not estimable
Subtotal (95% CI)		**2**		**2**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**30**		**25**	**100.0%**	**2.59 [1.19, 5.65]**
Total events	16		5			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%						



Appendix F – GRADE Tables

Results stratified according to the actual reductions in HbA1c reported at 3 months following treatment onset to determine the impact of rapid lowering of blood glucose on diabetic retinopathy outcomes.

F.1.1 Interventions with a HBa1c drop greater than 2% at 3 months

F.1.1.1 Intensified insulin treatment vs standard insulin therapy

Population with non-proliferative diabetic retinopathy

Table 15: Visual Acuity measured by a loss of two lines in one eye

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with standard insulin	Risk with Intensified insulin					
Visual Acuity at 7.5-year follow-up RR less than 1 favours intensified insulin treatment									
Reichard, 1993	RCT	89	38 per 100	14 per 100 (6 lower 33 higher)	Risk Ratio: 0.37 [0.16, 0.85]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study
2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)
Abbreviations: FU, follow up. Abbreviations: FU, follow up.

Table 16: Incidence of proliferative retinopathy or macular oedema

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with standard insulin	Risk with Intensified insulin					
Incidence of proliferative retinopathy or macular oedema at 7.5-year follow-up RR less than 1 favours intensified insulin treatment									
Reichard, 1993	RCT	89	57 per 100	29 per 100 (17 lower 49 higher)	Risk Ratio: 0.50 [0.29, 0.85]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study
2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)
Abbreviations: FU, follow up.

F.1.1.2 Multiple insulin injection therapy vs conventional insulin injection therapy

People with simple retinopathy

Table 17: Rates of Diabetic Retinopathy Severity Progression at 6-year FU

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with CIT	Risk with MIT					
Diabetic Retinopathy Severity Progression at 6-year follow-up RR less than 1 favours multiple insulin injection therapy									
Ohkubo, 1995	RCT	51	44 per 100	19 per 100 (8 lower 48 higher)	Risk Ratio: 0.44 [0.18, 1.08]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study
2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)
Abbreviations: FU, follow up.

Intensive insulin therapy vs insulin standard therapy for people with (People with minimal to moderate non proliferative retinopathy with a Fasting C-peptide levels >0.21 pmol/ml)

Table 18:Progression of retinopathy defined as a two or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 2-year FU

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
Progression of retinopathy defined as a two or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 2-year follow-up RR less than 1 favours intensive insulin therapy									
1 Emanuele 1996	RCT	97	31 per 100	25 per 100 (14 lower 46 higher)	Risk Ratio: 0.82 [0.46, 1.47]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study
2 Partially applicable
Abbreviations: FU, follow up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Standard	Risk Intensive					
Subgroup: Microaneurysm or mild DR 1 eye, no DR or microaneurysm only in other at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	892	8 per 100	3 per 100 (1 lower 5 higher)	Risk Ratio: 0.33 [0.17, 0.62]	serious[1]	N/A[2]	Sserious[3]	Low
Subgroup: Mild/moderate NPDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	386	12 per 100	9 per 100 (5 lower 16 higher)	Risk Ratio: 0.76 [0.42, 1.36]	serious[1]	N/A[2]	serious[3]	Low
Subgroup: Moderate/moderately severe NPDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	167	26 per 100	20 per 100 (11 lower 35 higher)	Risk Ratio: 0.77 [0.44, 1.36]	serious[1]	N/A[2]	serious[3]	Low
Subgroup: Severe NPDR or PDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	39	58 per 100	67 per 100 (41 lower 109 higher)	Risk Ratio: 1.14 [0.70, 1.87]	serious[1]	N/A[2]	serious[3]	Low

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	R
			Risk with Standard	Risk Intensive		

1 >33% of data from studies at moderate or high risk of bias due selective reporting of outcomes
2 Data from a single study
3 Partially applicable (study downgraded for indirectness, Subgroup with diabetic retinopathy included a large proportion (>50%) with Microaneurysm only non-proliferative retinopathy who are outside of the scope for this guideline)
Abbreviations: FU, follow up.

F.1.2 Interventions with a HBa1c drop greater than 2% at 3 months

F.1.2.1 Intensive glycaemic therapy vs Standard glycaemic therapy

Population with non-proliferative diabetic retinopathy

Table 19: Progression of 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)

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Standard	Risk Intensive					
Subgroup: Microaneurysm or mild DR 1 eye, no DR or microaneurysm only in other at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	892	8 per 100	3 per 100 (1 lower 5 higher)	Risk Ratio: 0.33 [0.17, 0.62]	Serious[1]	N/A[2]	Serious[3]	Low
Subgroup: Mild/moderate NPDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	386	12 per 100	9 per 100 (5 lower 16 higher)	Risk Ratio: 0.76 [0.42, 1.36]	Serious[1]	N/A[2]	Serious[3]	Low
Subgroup: Moderate/moderately severe NPDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye	RCT	167	26 per 100	20 per 100 (11 lower	Risk Ratio: 0.77 [0.44, 1.36]	Serious[1]	N/A[2]	Serious[3]	Low

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Standard	Risk Intensive					
Study, Chew, 2010)				35 higher)					
Subgroup: Severe NPDR or PDR at 4-year follow-up RR less than 1 favours intensive therapy									
1 (ACCORD Eye Study, Chew, 2010)	RCT	39	58 per 100	67 per 100 (41 lower 109 higher)	Risk Ratio: 1.14 [0.70, 1.87]	Serious[1]	N/A[2]	Serious[3]	Low

1 >33% of data from studies at moderate or high risk of bias due selective reporting of outcomes

2 Data from a single study

3 Partially applicable (study downgraded for indirectness, Subgroup with diabetic retinopathy included a large proportion (>50%) with Microaneurysm only non-proliferative retinopathy who are outside of the scope for this guideline)

Abbreviations: FU, follow up.

F.1.2.2 Intensive insulin treatment vs conventional treatment

Table 20: Progression of retinopathy defined as a three or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 9 years follow up

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
Rates of Diabetic Retinopathy Severity Progression (overall) at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	714	33 per 100	15 per 100 (8 lower 28 higher)	Risk Ratio: 1.02 [0.74, 1.40]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Very mild NPDR (20/20) at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	212	38 per 100	9 per 100 (5 lower 17 higher)	Risk Ratio: 1.03 [0.64, 1.67]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Mild NPDR (35/<35) at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	192	33 per 100	10 per 100 (5 lower 20 higher)	Risk Ratio: 1.02 [0.59, 1.76]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Moderate or severe NPDR (43/<43+) at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	70	45 per 100	44 per 100 (26 lower 74 higher)	Risk Ratio: 0.97 [0.49, 1.90]	No serious	N/A[1]	serious[2]	Moderate
1 Data from a single study									

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline) Abbreviations: FU, follow up.									

Table 21: Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
Loss of vision defined as (visual acuity, 20/200 or worse) at 9-year follow-up. RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	714	1 per 100	0 per 100 (0 lower 2 higher)	Risk Ratio: 0.14 [0.01, 2.66]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study
2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)
Abbreviations: FU, follow up.

Table 22:Incidence of macular oedema and clinically significant macular oedema as defined by the ETDRS. at 9-year follow-up

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
incidence of macular oedema at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	714	32 per 100	21 per 100 (16 lower 27 higher)	Risk Ratio: 0.66 [0.51, 0.85]	No serious	N/A[1]	serious[2]	Moderate
incidence of clinically significant macular oedema at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	714	17 per 100	12 per 100 (8 lower 17 higher)	Risk Ratio: 0.69 [0.49, 0.98]	No serious	N/A[1]	serious[2]	Moderate

1 Data from a single study

2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)

Abbreviations: FU, follow up.

F.1.3 Early worsening of retinopathy outcomes

F.1.3.1 Intensive Insulin Treatment Vs Conventional Treatment

Analysis of HbA1c reduction at 3 months: Intensive insulin treatment HbA1c: 8.2+(1.0) > 6.4S% vs Conventional Treatment HbA1c 8.3+(1.0) > 7.5%

Table 23: Early worsening of retinopathy defined as a three or more-step progression of retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at 6 months follow up

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
Subgroup: Very mild NPDR (20/<20) at 6 -months follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	240	1 per 100	6 per 100 1 lower 50 higher	Risk Ratio: 6.43 [0.83, 49.94]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Very mild NPDR (20/20) at 6 months at 9-year follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	212	7 per 100	9 per 100 4 lower 23 higher	Risk Ratio: 1.35 [0.53, 3.41]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Mild NPDR (35/<35) at 6-months follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	192	3 per 100	5 per 100 1 lower 21 higher	Risk Ratio: 1.77 [0.41, 7.70]	No serious	N/A[1]	serious[2]	Moderate
Subgroup: Moderate or severe NPDR (43/<43+) at 6- -months follow-up RR less than 1 favours intensive insulin treatment									

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
1 DCCT group, 1995	RCT	70	13 per 100	19 per 100 6 lower 56 higher	Risk Ratio: 1.43 [0.48, 4.24]	No serious	N/A[1]	serious[2]	Moderate
1 Data from a single study 2 Partially applicable Abbreviations: FU, follow up.									

Table 24: Clinically important early worsening of retinopathy at 6 months follow up.
Defined as development of severe non-proliferative diabetic retinopathy, proliferative retinopathy or clinically significant macula oedema as defined in the ETDRS

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
Clinically important Early worsening of retinopathy at 6 months follow-up RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	712	2 per 100	2 per 100 1 lower 7 higher	Risk Ratio: 1.44 [0.52, 4.01]	No serious	N/A	serious[2]	Moderate
Clinically important Early worsening of retinopathy at 12 months FU RR less than 1 favours intensive insulin treatment									
1 DCCT group, 1995	RCT	712	3 Per 100	2 per 100 1 lower 6 higher	Risk Ratio:] 0.96 [0.39, 2.39]	No serious	N/A	serious[2]	Moderate
1 Data from a single study 2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion									

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Risk with Intensive insulin					
(>50%) with Microaneurysm only who are outside of the scope for this guideline) Abbreviations: FU, follow up									

Table 25: Recovered from early worsening at next visit (6 and 12 month follow up)

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with conventional	Intensive insulin					
Recovered from Clinically important early worsening at next visit (6 month follow up)									
1 DCCT group, 1995	RCT	712	1 per 100	1 per 100 0 lower, 7 higher	Risk Ratio: 2.40 [0.47, 12.31]	No serious	N/A	serious[2]	Moderate
Recovered from Clinically important early worsening at next visit (12 month follow up)									
1 DCCT group, 1995	RCT	712	1 per 100	0 per 100 0 lower 3 higher	Risk Ratio: 0.32 [0.03, 3.07]	No serious	N/A	Serious[2]	
1 Data from a single study 2 Partially applicable (study downgraded for indirectness, Population with non-proliferative diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline) Abbreviations: FU, follow up.									

F.1.3.2 Continuous subcutaneous insulin infusion vs conventional injection treatment

People with non-proliferative diabetic retinopathy

Table 26:Progression of retinopathy at 8-month FU determined according to the ETDRS.

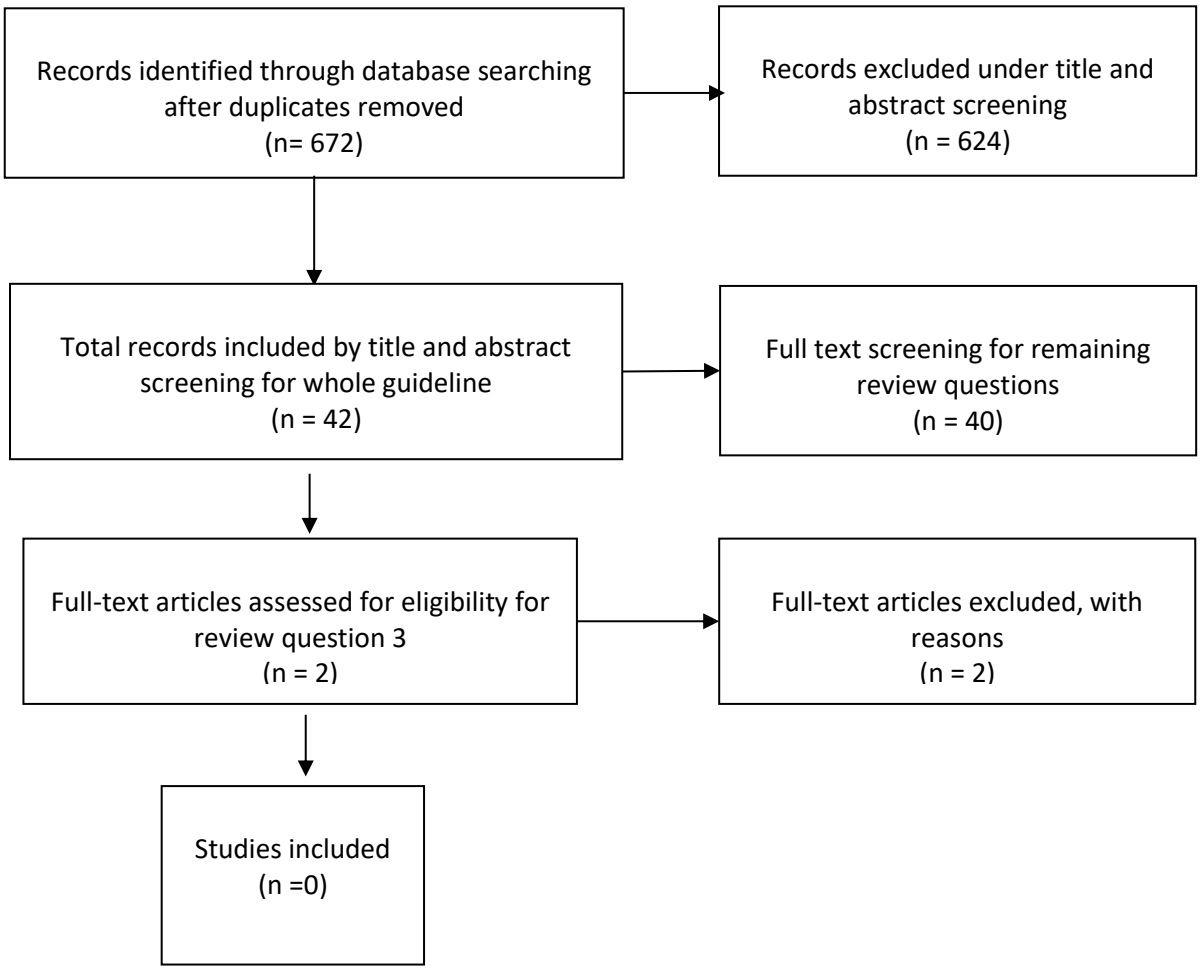
Analysis of HbA1c reduction at 3 months: Continuous insulin infusion: HbAlc level 10.3+(0.4) >8.2+(0.2) vs Conventional injection treatment: HbAlc level 10.1+ 0.3 > no significant change

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with CIT	Risk with CSII					
Rates of Diabetic Retinopathy Severity Progression (overall) at 8-month follow-up RR less than 1 favours continuous subcutaneous insulin infusion									
Kroc Collaborative Study, 1984	RCT	55	20 per 100	52 per 100 (24 lower 113 higher)	Risk Ratio: 2.59 [1.19, 5.65]	No serious	N/A	serious[2]	Moderate
Subgroup: Mild NPDR at 8-month follow-up RR less than 1 favours continuous subcutaneous insulin infusion									
Kroc Collaborative Study, 1984	RCT	27	33 per 100	87 per 100 (38 lower 198 higher)	Risk Ratio: 2.60 [1.14, 5.93]	No serious	N/A	serious[2]	Moderate
Subgroup: Moderate NPDR at 8-month follow-up RR less than 1 favours continuous subcutaneous insulin infusion									
Kroc Collaborative Study, 1984	RCT	24	9 per 100	23 per 100 (3 lower 191 higher)	Risk Ratio: 2.54 [0.31, 21.06]	No serious	N/A	serious[2]	Moderate
Subgroup: Severe NPDR or PDR 8-month follow-up RR less than 1 favours continuous subcutaneous insulin infusion									
Kroc Collaborative	RCT	4	Not estimable	Not estimable	No events	No serious	N/A[1]	serious[2]	Moderate

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with CIT	Risk with CSII					
Study, 1984									

1 Data from a single study
2 Partially applicable (study downgraded for indirectness, Subgroup with diabetic retinopathy included a large proportion (>50%) with Microaneurysm only who are outside of the scope for this guideline)
Abbreviations: FU, follow up.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

There are no included studies for this review question.

Appendix I – Health economic model

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

Appendix J – Excluded studies

Clinical evidence

Study	Reason
(1995) The effect of intensive diabetes therapy on the development and progression of neuropathy. Annals of Internal Medicine 122(8): 561-568	- Secondary publication of an included study that does not provide any additional relevant information
Abraira, C., Emanuele, N., Colwell, J. et al. (1992) Glycemic control and complications in type II diabetes: Design of a feasibility trial. Diabetes Care 15(11): 1560-1571	- Full text paper not available
ACCORD Study, Group, ACCORD Eye Study, Group, Chew, Emily Y et al. (2010) Effects of medical therapies on retinopathy progression in type 2 diabetes. The New England journal of medicine 363(3): 233-44	- Secondary publication of an included study that does not provide any additional relevant information
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	- Secondary publication of an included study that does not provide any additional relevant information
Aiello, L.P. (2014) Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 37(1): 17-23	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1982) Effect of 6 months of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. Steno study group. Lancet (London, England) 1(8264): 121-4	- Data not reported in an extractable format
Anonymous (1988) Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. The Kroc Collaborative Study Group. JAMA 260(1): 37-41	- Duplicate reference
Anonymous (1999) Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes care 22(1): 99-111	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional	- Does not contain a population of people with retinopathy at baseline

Study	Reason
treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet (London, England) 352(9131): 837-53	
Anonymous (1998) Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Archives of ophthalmology (Chicago, Ill. : 1960) 116(7): 874-86	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1996) The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes 45(10): 1289-98	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1995) The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial. Archives of ophthalmology (Chicago, Ill. : 1960) 113(1): 36-51	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1994) Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. The Journal of pediatrics 125(2): 177-88	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1995) The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44(8): 968-83	- Secondary publication of an included study that does not provide any additional relevant information
Arulanandham, A., Raju, A., Pradeep Rajkumar, L.A. et al. (2012) Prevalence of clinically significant macular edema [CSME] among glitazone users and non- users of type-2 DM patients with diabetic retinopathy. International Journal of Drug Development and Research 4(2): 132-137	- Not a relevant study design literature review
Azad, Nasrin, Agrawal, Lily, Emanuele, Nicholas V et al. (2014) Association of blood glucose control and pancreatic reserve with diabetic retinopathy in the Veterans Affairs Diabetes Trial (VADT). Diabetologia 57(6): 1124-31	- Data not reported in an extractable format
Barr, C C (2001) Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive insulin therapy, by The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N. Engl. J. Med 342:381-9, 2000. Survey of ophthalmology 45(5): 459-60	- Conference abstract

Study	Reason
Beulens, J W J, Patel, A, Vingerling, J R et al. (2009) Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. Diabetologia 52(10): 2027-36	- Does not contain a population of people with retinopathy at baseline
Brinchmann-Hansen, O, Dahl-Jorgensen, K, Hanssen, K F et al. (1988) Effects of intensified insulin treatment on retinal vessels in diabetic patients. The British journal of ophthalmology 72(9): 666-73	- Data not reported in an extractable format
Brinchmann-Hansen, O, Dahl-Jorgensen, K, Hanssen, K F et al. (1988) The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. Archives of ophthalmology (Chicago, Ill. : 1960) 106(9): 1242-6	- Data not reported in an extractable format
Brinchmann-Hansen, O, Dahl-Jorgensen, K, Hanssen, K F et al. (1985) Effects of intensified insulin treatment on various lesions of diabetic retinopathy. American journal of ophthalmology 100(5): 644-53	- Data not reported in an extractable format
Brinchmann-Hansen, O, Dahl-Jorgensen, K, Sandvik, L et al. (1992) Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study. BMJ (Clinical research ed.) 304(6818): 19-22	- Conference abstract
Canny, C L, Kohner, E M, Trautman, J et al. (1985) Comparison of stereofundus photographs in patients with insulin-dependent diabetes during conventional insulin treatment or continuous subcutaneous insulin infusion. Diabetes 34suppl3: 50-5	- Secondary publication of an included study that does not provide any additional relevant information
Chantelau, E and Kohner, E M (1997) Why some cases of retinopathy worsen when diabetic control improves. BMJ (Clinical research ed.) 315(7116): 1105-6	- Conference abstract
Chew, Emily Y, Ambrosius, Walter T, Howard, Letitia T et al. (2007) Rationale, design, and methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE). The American journal of cardiology 99(12a): 103i-111i	- Duplicate reference
Chung, Y.-R., Ha, K.H., Kim, H.C. et al. (2019) Dipeptidyl Peptidase-4 Inhibitors versus Other Antidiabetic Drugs Added to Metformin Monotherapy in Diabetic Retinopathy Progression: A real world-based cohort study. Diabetes and Metabolism Journal 43(5): 640-648	- Not a relevant study design Used real world evidence IPD

Study	Reason
Crepaldi, C., Nosadini, R., Bruttomesso, D. et al. (1989) The effect of continuous insulin infusion as compared with conventional insulin therapy in the evolution of diabetic retinal ischaemia. Two years report. Diabetes, Nutrition and Metabolism - Clinical and Experimental 2(3): 209-218	- Does not contain a population of people with retinopathy at baseline
Dahl-Jorgensen, K, Brinchmann-Hansen, O, Hanssen, K F et al. (1986) Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. British medical journal (Clinical research ed.) 293(6556): 1195-9	- Secondary publication of an included study that does not provide any additional relevant information
Dahl-Jorgensen, K, Brinchmann-Hansen, O, Hanssen, K F et al. (1985) Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. British medical journal (Clinical research ed.) 290(6471): 811-5	- Does not contain a population of people with retinopathy at baseline
de Oliveira Loureiro, Tomas, Cardoso, Joao Nobre, Lopes, Carlos Diogo Pinheiro Lima et al. (2021) The effect of insulin pump therapy in retinal vasculature in type 1 diabetic patients. European journal of ophthalmology 31(6): 3142-3148	- Does not contain a population of people with retinopathy at baseline
Diabetes Control and Complications Trial Research, Group (2000) Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes care 23(8): 1084-91	- Does not contain a population of people with retinopathy at baseline
Diabetes Control and Complications Trial Research, Group, Nathan, D M, Genuth, S et al. (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England journal of medicine 329(14): 977-86	- Does not contain a population of people with retinopathy at baseline
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research, Group, Lachin, John M, Genuth, Saul et al. (2000) Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The New England journal of medicine 342(6): 381-9	- Secondary publication of an included study that does not provide any additional relevant information
Duarte, L G, Figueira, J P, Nunes, S G et al. (2005) Intensified Multifactorial Intervention in Patients With Type 2 Diabetes Mellitus: Phenotypes of Retinopathy Progression. IOVS 46: ARVO E-abstract 366	- Full text paper not available

Study	Reason
Eschwege, E, Guyot-Argenton, C, Aubry, J P et al. (1976) Effect of multiple daily insulin injections on the course of diabetic retinopathy. Diabetes 25(5): 463-9	- Data not reported in an extractable format
Feman, SS, Leonard-Martin, TC, Klein, R et al. (1998) CHANGES IN DIABETIC RETINOPATHY(DR) IN rhIGF-I CO-THERAPY WITH INSULIN IN TYPE I DM. IOVS 39: arvoabstract921	- Full text paper not available
Friberg, T R, Rosenstock, J, Sanborn, G et al. (1985) The effect of long-term near normal glycemic control on mild diabetic retinopathy. Ophthalmology 92(8): 1051-8	- Does not contain a population of people with retinopathy at baseline
Gaede, P, Vedel, P, Parving, H H et al. (1999) Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet (London, England) 353(9153): 617-22	- Does not contain a population of people with retinopathy at baseline
Gaede, PH, Jepsen, PV, Parving, HH et al. (1999) Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno-2 study. Ugeskrift for laeger 161(30): 4277-4285	- Does not contain a population of people with retinopathy at baseline
Genuth, Saul (2006) Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 12suppl1: 34-41	- Full text paper not available
Hanssen, KF, Brinchmann-Hansen, O, Dahl-Jørgensen, K et al. (1988) Effect of intensive treatment on diabetic retinopathy. Journees annuelles de diabetologie de l'Hotel-Dieu: 167-173	- Full text paper not available
Helve, E, Laatikainen, L, Merenmies, L et al. (1987) Continuous insulin infusion therapy and retinopathy in patients with type I diabetes. Acta endocrinologica 115(3): 313-9	- Does not contain a population of people with retinopathy at baseline
Henricsson, M, Nilsson, A, Janzon, L et al. (1997) The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin-dependent diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association 14(2): 123-31	- Does not contain a population of people with retinopathy at baseline

Study	Reason
Holman, R.R., Dornan, T.L., Mayon-White, V. et al. (1983) Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet 1(8318): 204-208	- Full text paper not available
Huri, H.Z., Huey, C.C., Mustafa, N. et al. (2018) Association of glycemic control with progression of diabetic retinopathy in type 2 diabetes mellitus patients in Malaysia. Brazilian Journal of Pharmaceutical Sciences 54(2): e17484	- Review article but not a systematic review
Ismail-Beigi, Faramarz, Craven, Timothy, Banerji, Mary Ann et al. (2010) Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet (London, England) 376(9739): 419-30	- Does not contain a population of people with retinopathy at baseline
Jacobson, A.M., Braffett, B.H., Cleary, P.A. et al. (2013) The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: A 23-year follow-up of the diabetes control and complications/ epidemiology of diabetes interventions and complications cohort. Diabetes Care 36(10): 3131-3138	- Does not contain a population of people with retinopathy at baseline
Kang, E.Y.-C., Kang, C., Wu, W.-C. et al. (2021) Association between add-on dipeptidyl peptidase-4 inhibitor therapy and diabetic retinopathy progression. Journal of Clinical Medicine 10(13): 2871	- Does not contain a population of people with retinopathy at baseline
KCT0002681 (2018) Effects of anti-hyperglycemic agents on diabetic retinopathy. https://trialsearch.who.int/Trial2.aspx?TrialID=KCT0002681	- Not a relevant study design literature review
Kohner, E M (2008) Microvascular disease: what does the UKPDS tell us about diabetic retinopathy?. Diabetic medicine : a journal of the British Diabetic Association 25suppl2: 20-4	- Review article but not a systematic review
Laatikainen, L, Teramo, K, Hieta-Heikurainen, H et al. (1987) A controlled study of the influence of continuous subcutaneous insulin infusion treatment on diabetic retinopathy during pregnancy. Acta medica Scandinavica 221(4): 367-76	- Does not contain a population of people with retinopathy at baseline
Lam, P.Y., Chow, S.C., Lam, W.C. et al. (2021) Management of patients with newly diagnosed diabetic mellitus: Ophthalmologic outcomes in intensive versus conventional glycemic control. Clinical Ophthalmology 15: 2767-2785	- Duplicate reference

Study	Reason
Lauritzen, T, Frost-Larsen, K, Larsen, H W et al. (1983) Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. Lancet (London, England) 1(8318): 200-4	- Does not contain a population of people with retinopathy at baseline
Lauritzen, T, Frost-Larsen, K, Larsen, H W et al. (1985) Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes 34suppl3: 74-9	- Secondary publication of an included study that does not provide any additional relevant information
Liu, Yuqi, Li, Juan, Ma, Jinfang et al. (2020) The Threshold of the Severity of Diabetic Retinopathy below Which Intensive Glycemic Control Is Beneficial in Diabetic Patients: Estimation Using Data from Large Randomized Clinical Trials. Journal of diabetes research 2020: 8765139	- Review article but not a systematic review
Marchand, L; Luyton, C; Bernard, A (2021) Glucagon-like peptide-1 (GLP-1) receptor agonists in type 2 diabetes and long-term complications: FOCUS on retinopathy. Diabetic medicine : a journal of the British Diabetic Association 38(1): e14390	- Review article but not a systematic review
Mohan, R., Mohan, V., Ramachandran, A. et al. (1989) Use of monocomponent insulins and the course of diabetic retinopathy - A follow-up study. Journal of the Diabetic Association of India 29(2): 55-58	- Study does not contain a relevant intervention
Nathan, D.M. (2014) The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. Diabetes Care 37(1): 9-16	- Duplicate reference
Patel, A., MacMahon, S., Chalmers, J. et al. (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 358(24): 2560-2572	Review article but not a systematic review
Reichard, P (1995) Are there any glycemic thresholds for the serious microvascular diabetic complications?. Journal of diabetes and its complications 9(1): 25-30	- Data not reported in an extractable format
Reichard, P, Berglund, B, Britz, A et al. (1991) Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. Journal of internal medicine 230(2): 101-8	- Data not reported in an extractable format

Study	Reason
Reichard, P, Britz, A, Carlsson, P et al. (1990) Metabolic control and complications over 3 years in patients with insulin dependent diabetes (IDDM): the Stockholm Diabetes Intervention Study (SDIS). Journal of internal medicine 228(5): 511-7	- Secondary publication of an included study that does not provide any additional relevant information
Reichard, P, Britz, A, Cars, I et al. (1988) The Stockholm Diabetes Intervention Study (SDIS): 18 months' results. Acta medica Scandinavica 224(2): 115-22	- Secondary publication of an included study that does not provide any additional relevant information
Reichard, P; Britz, A; Rosenqvist, U (1991) Intensified conventional insulin treatment and neuropsychological impairment. BMJ (Clinical research ed.) 303(6815): 1439-42	- Full text paper not available
Reid, Laura J, Gibb, Fraser W, Colhoun, Helen et al. (2021) Continuous subcutaneous insulin infusion therapy is associated with reduced retinopathy progression compared with multiple daily injections of insulin. Diabetologia 64(8): 1725-1736	- Does not contain a population of people with retinopathy at baseline
Rosenstock, J; Friberg, T; Raskin, P (1986) Effect of glycemic control on microvascular complications in patients with type I diabetes mellitus. The American journal of medicine 81(6): 1012-8	- Does not contain a population of people with retinopathy at baseline
Secchi, A and Pastore, MR (1993) A preliminary report on diabetes control and complication trial (DCCT). Italian journal of ophthalmology 7(3): 163-166	- Secondary publication of an included study that does not provide any additional relevant information
Shichiri, M, Kishikawa, H, Ohkubo, Y et al. (2000) Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes care 23suppl2: b21-9	- Secondary publication of an included study that does not provide any additional relevant information
Tovi, J; Ingemansson, S O; Engfeldt, P (1998) Insulin treatment of elderly type 2 diabetic patients: effects on retinopathy. Diabetes & metabolism 24(5): 442-7	- Does not contain a population of people with retinopathy at baseline
Varadhan, Lakshminarayanan, Humphreys, Tracy, Walker, Adrian B et al. (2014) The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes research and clinical practice 103(3): e37-9	- Not a relevant study design literature review
Wang, P H; Lau, J; Chalmers, T C (1993) Metaanalysis of the effects of intensive glycemic control on late complications of type I diabetes mellitus. The Online journal of current clinical trials docno60	- Systematic review used as source of primary studies

Study	Reason
	- Not a relevant study design
White, N H, Cleary, P A, Dahms, W et al. (2001) Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). The Journal of pediatrics 139(6): 804-12	- Secondary publication of an included study that does not provide any additional relevant information
White, Neil H, Sun, Wanjie, Cleary, Patricia A et al. (2008) Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Archives of ophthalmology (Chicago, Ill. : 1960) 126(12): 1707-15	- Full text paper not available
White, Neil H, Sun, Wanjie, Cleary, Patricia A et al. (2010) Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. Diabetes 59(5): 1244-53	- Secondary publication of an included study that does not provide any additional relevant information
Writing Team for the DCCT/EDIC Research, Group, Gubitosi-Klug, Rose A, Sun, Wanjie et al. (2016) Effects of Prior Intensive Insulin Therapy and Risk Factors on Patient-Reported Visual Function Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. JAMA ophthalmology 134(2): 137-45	- Data not reported in an extractable format
Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research, Group (2002) Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 287(19): 2563-9	- Secondary publication of an included study that does not provide any additional relevant information
Zoungas, Sophia, Arima, Hisatomi, Gerstein, Hertzel C et al. (2017) Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. The lancet. Diabetes & endocrinology 5(6): 431-437	- Full text paper not available

Economic evidence

Title	Reason for exclusion
Polak, B C P, Crijns, H, Casparie, A F et al. (2003) Cost-effectiveness of glycemic control and ophthalmological care in	- Exclude - diabetes only not diabetic retinopathy

Title	Reason for exclusion
diabetic retinopathy. Health policy (Amsterdam, Netherlands) 64(1): 89-97	
Ratner, R E (2001) Glycemic control in the prevention of diabetic complications. Clinical cornerstone 4(2): 24-37	- Exclude - diabetes only not diabetic retinopathy

Appendix K – Research recommendations – full details

K.1.1.1 Research recommendation

In people experiencing a rapid substantial reduction in HbA1c, what is the risk of short-term progression of diabetic retinopathy or diabetic macular oedema, and is there a risk of long-term visual loss?

K.1.1.2 Why this is important

There are a number of treatments for diabetes that work to intensively reduce blood glucose levels. There is limited evidence investigating the effects of these treatments on early worsening of retinopathy or maculopathy. More, high quality, evidence is needed to determine what short-term effects are associated with these treatments, particularly in relation to their potential effects on early worsening of diabetic retinopathy or macular oedema. Research should also consider if these effects are sustained over time, or if they are reversible.

K.1.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the short-term risks to vision associated with intensive blood glucose reduction therapies. Research can help identify the extent of these risks, and whether people who are having treatment to intensively reduce blood glucose levels should have additional monitoring or treatment for their retinopathy or maculopathy.
Relevance to NICE guidance	Intensive glucose reduction has been considered in this guideline and there is a lack of data on short term safety for treatments used in current practice.
Relevance to the NHS	The outcome would affect how people who need to rapidly to reduce their blood glucose levels are treated and monitored, A greater understanding of early worsening may reduce the number of people who need additional treatment for its associated effects.
National priorities	Moderate
Current evidence base	6 RCTs, 1 partly based in the UK. Studies provide limited short-term data for current treatments.
Equality considerations	None known

K.1.1.4 Modified PICO table

Population	• People with non-proliferative and proliferative diabetic retinopathy • People with diabetic macular oedema

Intervention	Studies where the stated aim is to intensively lower blood glucose. For example: • Glucagon-like peptide 1 receptor agonist • Pioglitazone • Insulin pump therapy • Injected insulin • Sulfonylurea • SGLT-2 inhibitors • Very low-calorie diet • Treatment intensification to achieve lower glucose targets (for example, by increasing treatment dose)
Comparator	Standard therapy
Outcome	At 3 months, 6 months, and 12 months • Progression of diabetic retinopathy • Best corrected visual acuity • Incidence of macular oedema • Progression of macular oedema • Quality of life • Reduction of HbA1c
Study design	RCT
Timeframe	Short term and long term
Additional information	Subgroups should be used to consider whether the effects are different for different groups (e.g. those with higher or lower HbA1c at baseline)