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Drug treatments for managing cystic fibrosis-related diabetes (Review)

Onady GM, Stolfi A

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[Intervention Review]

Drug treatments for managing cystic fibrosis-related diabetes

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ABSTRACT

Background

The Cystic Fibrosis Foundation recommends both short-term and long-acting insulin therapy when cystic fibrosis-related diabetes (CFRD) has been diagnosed. Diagnosis is based on: an elevated fasting blood glucose level greater than 6.94 mmol/L (125 mg/dL); or oral glucose tolerance tests greater than 11.11 mmol/L (200 mg/dL) at two hours; or symptomatic diabetes for random glucose levels greater than 11.11 mmol/L (200 mg/dL); or glycated hemoglobin levels of at least 6.5%. This is an update of a previously published review.

Objectives

To establish the effectiveness of insulin and oral agents for managing diabetes in people with cystic fibrosis in relation to blood sugar levels, lung function and weight management.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. We also handsearched abstracts from pulmonary symposia and the North American Cystic Fibrosis Conferences.

Date of most recent register search: 10 September 2020.

We searched online trials registries; date of most recent searches: 21 March 2020.

Selection criteria

Randomized controlled trials comparing all methods of pharmacological diabetes therapy in people with diagnosed CFRD.

Data collection and analysis

Two authors independently extracted data and assessed the risk of bias in the included studies. Authors also used GRADE to assess the quality of the evidence.

Main results

The searches identified 29 trials (45 references). Four included trials provide results: one short-term single-center cross-over trial (seven adults) comparing insulin with oral repaglinide and no medication in adults with CFRD and normal fasting glucose; one long-term multicenter trial (61 adults with CFRD) comparing insulin with oral repaglinide and placebo; one long-term multicenter trial (67 adults) comparing insulin with oral repaglinide; and one 12-week single-center cross-over trial (20 adults) comparing the long-acting insulin glargine to short-term neutral protamine Hagedorn insulin. Two ongoing trials of newly approved incretin mimics have been noted for possible future inclusion.

Downgrading of the quality of the evidence was mainly due to risks of bias across all domains, but particularly due to concerns surrounding allocation concealment and selective reporting. There were also some concerns due to imprecision from small sample sizes and low event rates. Finally, there may be some bias due to the amounts of insulin and repaglinide given not being comparable.

Data from one trial comparing insulin to placebo (39 participants) did not show any difference between groups for the primary outcomes of blood glucose levels (very low-quality evidence), lung function (low-quality evidence) or nutritional status (low-quality evidence). Similarly, no differences between groups were seen for the secondary outcomes of number of hypoglycemic episodes (low-quality evidence), secondary infection complications or quality of life (QoL). These results were mirrored in the narrative reports for the second trial in this comparison (seven participants).

Data from the one-year trial comparing repaglinide to placebo (38 participants), showed no differences between groups for the primary outcomes of blood glucose levels (very low-quality evidence), lung function (low-quality evidence) and nutritional status (low-quality evidence). Also, no differences were seen between groups for the secondary outcomes of number of hypoglycemic episodes (low-quality evidence), secondary infection complications or QoL. These findings were mirrored in the narrative reports for the second trial (n = 7) in this comparison.

Three trials compared insulin to repaglinide (119 participants). Data from one trial (n = 67) showed no difference in blood glucose levels at either 12 months (high-quality evidence) or 24 months; narrative reports from one trial (45 participants) reported no difference between groups, but the second trial (7 participants) reported a beneficial effect of insulin over repaglinide. Two trials (112 participants) found no difference between insulin and repaglinide in lung function or nutritional status (moderate-quality evidence). Two trials (56 participants) reported no difference in the number of hypoglycemic episodes (low-quality evidence). One trial (45 participants) reported no difference between groups in secondary infections and cystic fibrosis QoL.

The single trial comparing glargine to neutral protamine Hagedorn insulin did not report directly on the review's primary outcomes, but did report no differences between groups in post-prandial glucose values and weight; neither group reported infectious complications. There was no difference in episodes of hypoglycemia (very low-quality evidence) and while there was no difference reported in QoL, all participants opted to continue treatment with glargine after the trial was completed.

Mortality was not reported by any trial in any comparison, but death was not given as a reason for withdrawal in any trial.

Authors' conclusions

This review has not found any conclusive evidence that any agent has a distinct advantage over another in controlling hyperglycemia or the clinical outcomes associated with CFRD. Given the treatment burden already experienced by people with cystic fibrosis, oral therapy may be a viable treatment option.

While some cystic fibrosis centers use oral medications to help control diabetes, the Cystic Fibrosis Foundation (USA) clinical practice guidelines support the use of insulin therapy and this remains the most widely-used treatment method. Randomized controlled trials specifically related to controlling diabetes and its impact on the course of pulmonary disease process in cystic fibrosis continue to be a high priority. Specifically, investigators should evaluate adherence to different therapies and also whether there is benefit in using additional hypoglycemic agents as well as the newly approved incretin mimics. Agents that potentiate insulin action, especially agents with additional anti-inflammatory potential should also be further investigated as adjuvant therapy to insulin.

PLAIN LANGUAGE SUMMARY

Drug treatments for managing cystic fibrosis-related diabetes

Review question

We reviewed the evidence regarding different drugs for managing cystic fibrosis-related diabetes (CFRD).

Background

Cystic fibrosis (CF) is a common life-limiting genetic condition, mainly causing damage to the lungs and pancreas. The pancreas makes insulin, a hormone which the body needs to take sugar into the cells so it can be converted into energy. In up to 90% of people with CF, problems with the pancreas and digestive enzymes mean nutrients are not properly absorbed. People with CF need high-calorie and high-protein diets to provide enough energy to maintain muscle mass so as to support their breathing and make up for breathing difficulties from disease-damaged lungs. It is important for people with CF to turn sugar into energy efficiently. This is especially challenging for people with CFRD because damage to the pancreas affects insulin production and release. Inflammation seen in CF can reduce insulin production and lessen its effect by causing insulin resistance. Increased life expectancy for people with CF means that 50% of adults with CF are likely to develop CFRD.

We wanted to assess different treatments for CFRD to limit any related decline in health. These include artificial sources of insulin (like long-acting glargine or short-acting protamine insulin), the control of natural hormones that stimulate insulin release and medications that enhance a person’s own insulin release or affect insulin resistance.

Search date

The evidence is current to: 10 September 2020.

Study characteristics

We included four trials (145 adults). Two trials compared insulin to either no treatment for two months (seven participants) or to a placebo (dummy drug with no active medication) for one year (61 participants). These trials, along with a third trial lasting two years (67 adults), also compared insulin (given via a syringe) to repaglinide tablets. The fourth trial (20 participants) compared the long-acting insulin glargine to short-term neutral protamine Hagedorn insulin over a 12-week period.

Key results

We found results for our primary outcomes of blood glucose levels, lung function and nutritional status and our secondary outcomes of pulmonary exacerbations (flare up of disease), complications and quality of life. We could only analyse limited results and did not find evidence that showed that any one treatment was better than another. Our analysis did not show that either insulin or repaglinide made any difference to any of our outcomes compared to placebo or no treatment at any time point. Similarly, most of our results did not show whether insulin or repaglinide was better, but the evidence was a little stronger that there was no difference in lung function, nutritional status or blood glucose levels at 12 months. Similarly, the evidence was not strong enough to show if there is any difference between glargine and neutral protamine Hagedorn insulin for any of our outcome measures. None of the trials reported if there were any deaths.

Given the treatment burden already experienced by people with CF, tablets may be a welcome alternative to injecting insulin. Longer-term trials with larger numbers of people are still needed to see how controlling CFRD affects lung function. Investigators should also assess how many people keep to their treatment plan when comparing insulin to tablets. Research should look at using the drugs by themselves or together with insulin to enhance insulin action, especially those agents with additional anti-inflammatory potential.

Quality of the evidence

We had some concerns about the quality of the evidence; mainly that there would be bias because clinicians probably knew in advance which treatment group the next person was going to be put into (e.g. healthier participants might be put into one group to show better results for that treatment) or bias from people taking part knowing which treatment group they were in (e.g. insulin via a syringe or repaglinide as a tablet). There may also be bias because results may only be selectively reported. We had some concerns that the analysis would not be precise due to small numbers of participants and low event rates. Finally, there may be bias in the results as the amounts of insulin and repaglinide given were not comparable.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: insulin versus placebo for CFRD

Insulin versus placebo for cystic fibrosis-related diabetes

Patient or population: adults with CFRD

Settings: outpatients

Intervention: insulin (0.5 unit insulin aspart/15 g dietary carbohydrate) 3 times daily

Comparison: oral placebo 3 times daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Insulin				
HbA1c	1 study reported that HbA1C levels did not significantly change in either the insulin or the placebo group (Moran 2009).		N/A	39 (1)	⊕⊖⊖⊖ **very low[a,c]**	No data were available for this outcome and results have been reported narratively (Moran 2009). One trial (n = 7) reported that there was a benefit seen glucose AUC (reduction) at both the two-hour time point (P < 0.05) and the five-hour time point (P < 0.05) (Moran 2001)
FEV_1 % predicted: change from baseline Follow-up: 12 months	The mean change in FEV_1 % predicted in the control group was - 3% predicted.	The mean change in FEV_1 % predicted in the intervention group was 1.2% higher (5.6% lower to 8.0% higher).	**MD** 1.20 (-5.63 to 8.03)	39 (1)	⊕⊕⊖⊖ **low[b,c]**	No difference was observed between groups, P = 0.3 for overall effect (Moran 2009).
FVC % predicted: change from baseline Follow-up: 12 months	The mean change in FVC % predicted in the control group was -1.1% predicted.	The mean change in FVC % predicted in the intervention group was 0.6% higher (5.7% lower to 6.9% higher).	**MD** 0.60 (-5.67 to 6.87)	39 (1)	⊕⊕⊖⊖ **low[b,c]**	No difference was observed between groups, P = 0.85 for overall effect (Moran 2009).

BMI (kg/m²): change from baseline Follow-up: 12 months	The mean change in BMI in the control group was -0.02 kg/m².	The mean change in BMI in the intervention groups was 0.41 kg/m² higher (0.23 kg/m² lower to 1.1 kg/m² higher)	**MD** 0.41 (-0.23 to 1.05)	39 (1)	⊕⊕⊖⊖ **low**[b,c]	There was no significant difference between the placebo group and intervention group, P = 0.21 for overall effect (Moran 2009).
Hypoglycemia: number of episodes Follow-up: 3 months	There were no hypoglycemic events in the placebo group, therefore it is not possible to calculate the corresponding risk.		**RR** 9.23 (0.53 to 159.14)	55 (1)	⊕⊕⊖⊖ **low**[b,d]	There was no significant difference between groups after 3 months, but it is not clear whether the hypoglycemic events occurred in those with CFRD or those with impaired glucose tolerance (Moran 2009). The earlier Moran trial (n = 7) reported hypoglycemic events at 2 months and these data did not give a significant result, RR 2.00 (95% CI 0.23 to 17.34) (Moran 2001).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFRD**: cystic fibrosis-related diabetes; **CI**: confidence interval; **HbA1c**: glycated hemoglobin; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias in the included study, particularly around the domains of allocation concealment and selective outcome reporting. No data were reported for this outcome.
b. Downgraded once due to an unclear risk of bias in the single included study. Although the study was deemed to be at low risk across the domains of randomization and blinding, the allocation process was not clearly described. The study was also deemed to be at high risk of bias due to selective reporting, although that does not affect this particular outcome.
c. Downgraded once due to imprecision from small sample size; one study was 3-armed study which therefore reduces the number of participants in each arm.
d. Downgraded once due to imprecision from both small sample size and low event rates.

Summary of findings 2. Summary of findings: repaglinide versus placebo for CFRD

Repaglinide versus placebo for CFRD
Patient or population: adults with CFRD

Settings: outpatients

Intervention: repaglinide (2.0 mg) orally 3 times daily

Comparison: oral placebo 3 times daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Repaglinide				
HbA1c Follow-up: 12 months	1 trial reported that HbA1C levels did not significantly change in either the repaglinide or the placebo group (Moran 2009).		N/A	38 (1)	⊕⊖⊖⊖ **very low**[a,b]	No data were available for this outcome and results have been reported narratively (Moran 2009).
FEV_1 % predicted; change from baseline Follow-up: 12 months	The mean change in FEV_1 % predicted in the control group was -3% predicted.	The mean change in FEV_1 % predicted in the intervention group was 1.7% higher (5.1% lower to 8.5% higher).	**MD** 1.70 (-5.13 to 8.53)	38 (1)	⊕⊕⊖⊖ **low**[b,c]	No difference was observed between groups, P = 0.6 for overall effect (Moran 2009).
FVC % predicted: change from baseline Follow-up: 12 months	The mean change in FVC % predicted in the control group was -1.1% predicted.	The mean change in FVC % predicted in the intervention groups was 1.0% higher (7.4% lower to 5.4% higher).	**MD** -1.00 (-7.40 to 5.40)	38 (1)	⊕⊕⊖⊖ **low**[b,c]	No difference was observed between groups, P = 0.76 for overall effect (Moran 2009).
BMI (kg/m^2): change from baseline Follow-up: 12 months	The mean change in BMI in the control group was -0.02 kg/m^2.	The mean change in BMI in the intervention groups was 0.2 kg/m^2 higher (0.5 kg/m^2 lower to 0.8 kg/m^2 higher).	**MD** 0.17 (-0.47 to 0.81)	38 (1)	⊕⊕⊖⊖ **low**[b,c]	There was no significant difference between the placebo group and intervention group, P = 0.6 for overall effect (Moran 2009).
Hypoglycemia: number of episodes Follow-up: 3 months	There were mild hypoglycemic events reported in 23% of repaglinide participants, but no placebo participants reported hypoglycemia (P < 0.04); therefore it is not possible to calculate the corresponding risk.		**RR** 12.52 (0.74 to 211.20)	51 (1)	⊕⊖⊖⊖ **very low**[a,d]	The earlier Moran study also reported on this outcome but at 2 months. These data did not give a significant result, RR 2.00 (95% CI 0.23 to 17.34) (Moran 2001).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFRD**: cystic fibrosis-related diabetes; **CI**: confidence interval; **HbA1c**: glycated hemoglobin; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias in the included study, particularly around the domains of allocation concealment and selective outcome reporting. No data were reported for this outcome.
b. Downgraded once due to imprecision from small sample size. This was a 3-armed study which therefore reduces the number of participants in each arm.
c. Downgraded once due to an unclear risk of bias in the single included trial. Although the study was deemed to be at low risk across the domains of randomisation and blinding, the allocation process was not clearly described. The trial was also deemed to be at high risk of bias due to selective reporting although that does not affect this particular outcome.
d. Downgraded once due to imprecision from both small sample size and low event rates.

Summary of findings 3. Summary of findings: repaglinide versus insulin for CFRD

Repaglinide versus insulin for CFRD

Patient or population: children over 12 and adults with CFRD

Settings: home

Intervention: oral repaglinide (0.5 mg - 2 mg) 3 times daily

Comparison: insulin 3 times daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Insulin	Repaglinide				
HbA1c (%) change from baseline Follow-up: 12 months	The mean change in HbA1c in the control group was -0.1%.	The mean change in HbA1c in the intervention group was 0.3% higher (0.14% lower to 0.74% higher).	**MD** 0.30 (-0.14 to 0.74)	67 (1)	⊕⊕⊕⊕ **high**	Ballmann also reported the change from baseline in HbA1c at 24 months, but found no significant difference between groups MD 0.4% (95% CI -0.09 to 0.89) (Ballmann 2018b).

FEV_1 % predicted change from baseline Follow-up: 12 months	The mean change in FEV_1 % predicted ranged across control groups from -1.8% to -1.7%.	The mean FEV_1 in the intervention groups was 0.51% lower (4.22% lower to 3.2% higher).	**MD** -0.51 (-4.22 to 3.20)	112 (2)	⊕⊕⊕⊖ **moderate**[a]	The Ballmann study also reported this outcome at 24 months, but found no significant difference between groups MD -0.10% predicted (95% CI -4.12 to 3.92) (Ballmann 2018b).
FVC % predicted change from baseline Follow-up: 12 months	The mean change in FVC % predicted ranged across control groups from -0.8% to -0.5%.	The mean change in FVC % predicted in the intervention groups was 1.0% lower (4.29% lower to 2.3% higher).	**MD** -1.00 (-4.29 to 2.29)	112 (2)	⊕⊕⊕⊖ **moderate**[a]	The Ballmann study also reported this outcome at 24 months, but found no significant difference between groups MD -3.40% predicted (95% CI -7.37 to 0.57) (Ballmann 2018b).
BMI (kg/m^2) change from baseline Follow-up: 12 months	The mean change in BMI kg/m^2 in the control group was 0.15 kg/m^2.	The mean change in the intervention group was 0.24 kg/m^2 higher (0.34 kg/m^2 lower to 0.82 kg/m^2 higher).	**MD** 0.24 (-0.34 to 0.82)	45 (1)	⊕⊕⊖⊖ **low**[b,c]	A further trial reported BMI z score and found no significant improvement in z score in the repaglinide treatment group compared to insulin at 12 months (n = 67), MD 0.00 (95%CI -0.49 to 0.49). This difference remained non-significant at 24 months (n = 67), MD 0.40 (95% CI -0.09 to 0.89) (Ballmann 2018b).
Hypoglycemia number of episodes Follow-up: 3 months	**167 per 1000**	**230 per 1000** (80 to 670)	**RR** 1.38 (0.48 to 4.01)	56 (2)	⊕⊕⊖⊖ **low**[b,c]	The earlier Moran trial also reported on episodes of hypoglycaemia over 2 months, but reported no significant differences between groups, RR 0.50 (95% CI 0.06 to 4.33) (Moran 2001).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFRD**: cystic fibrosis-related diabetes; **CI**: confidence interval; **HbA1c**: glycated hemoglobin; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded once due to risk of bias within the included studies. The larger Ballmann study was at low of risk of bias across most domains but was deemed to be at high risk of performance bias due to the study being open-label. The Moran study was at high or unclear risk of bias across 3 domains and so, when taken together, there was enough risk of bias to affect the results.
b. Downgraded once due to an unclear risk of bias in the single included study. Although the study was deemed to be at low risk across the domains of randomisation and blinding, the allocation process wasn't clearly described. The study was also deemed to be at high risk of bias due to selective reporting although that does not affect this particular outcome.
c. Downgraded once due to imprecision from small sample size. This was a 3-armed study which therefore reduces the number of participants in each arm.

Summary of findings 4. Summary of findings: NPH insulin versus glargine for CFRD

NPH insulin versus glargine for CFRD

Patient or population: adults with CFRD and fasting hyperglycemia

Settings: home

Intervention: NPH insulin (individually dosed based on insulin to carbohydrate ratio) at bedtime

Comparison: insulin glargine given at bedtime

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Insulin glargine	NPH insulin				
HbA1c	This outcome was not measured.					1 study reported on fasting and 2-hour post-prandial glucose. There was no significant difference between groups for either measure, MD 10.00 mg/dL (95% CI -12.86 to 32.86) and MD 8.00 mg/dL (95% CI -10.07 to 26.07) respectively (Grover 2008).
FEV_1 % predicted	This outcome was not measured.					
FVC % predicted	This outcome was not measured.					
BMI kg/m²	This outcome was not measured.					BMI was not reported for this comparison. The Grover study did however report on mean change in: weight, MD -1.00 kg (95% CI -2.39 to 0.39); fat mass, MD -0.30 kg (95% CI -1.41 to 0.81); and lean mass, MD -0.20 kg (95% CI -0.75 to 0.35). None of the results

					showed any significant difference between NPH insulin and glargine (Grover 2008).
Hypoglycemia mean number of events per participant Follow-up: 12 weeks	The mean number of hypoglycaemic events in the control group was 6 per participant.	The mean number of hypoglycaemic events in the intervention group was 1 event lower (4 events lower to 2 events higher).	**MD** -1.00 (-3.77 to 1.77)	19 (1)	⊕⊖⊖⊖ **very low**[a,b]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFRD**: cystic fibrosis-related diabetes; **CI**: confidence interval; **HbA1c**: glycated hemoglobin; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NPH**: neutral protamine hagedorn.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice for risk of bias. There was an unclear or high risk of bias across all domains for this study.
b. Downgraded once due to imprecision caused by small sample size and low event rates.

BACKGROUND

Description of the condition

Survival of people with cystic fibrosis (pwCF) now extends well into adulthood, and as a consequence secondary disease processes are increasingly being recognized. Cystic fibrosis-related diabetes (CFRD) represents the highest secondary prevalence in cystic fibrosis (CF) and is seen in nearly 20% of adolescents and 40% to 50% of adults with CF (Moran 2009). The diagnosis of CFRD is currently made during a period of stable baseline health according to standard American Diabetic Association (ADA) criteria. This diagnosis is therefore made if the two-hour oral glucose tolerance plasma glucose is elevated (greater than or equal to 200 mg/dL (11.1 mmol/L)); there is a fasting plasma glucose greater than or equal to 126; A1C is greater than or equal to 6.5%; or if polyuria or polydipsia are in the presence of a casual glucose level of greater than or equal to 200 mg/dL. The diagnosis of CFRD can additionally be considered in pwCF with acute illness when they maintain fasting plasma glucose elevations, or two-hour post-prandial plasma glucose levels greater than or equal to 200 mg/dL for more than 48 hours (Moran 2010). There is a 36% occurrence of microvascular complications that includes kidney disease and retinopathy in CFRD, compared to 18% in the non-CF diabetic population (Landers 1997; Schwarzenberg 2007). Microvascular complications result from prolonged periods of hyperglycemia which inflict pathological changes within small blood vessels. These factors may impact on a reported 60% survival to age 30 years for pwCF but without diabetes, compared to 25% for pwCF and diabetes (Finkelstein 1988). The negative impact of diabetes has been more specifically linked to rapid decline in pulmonary function and body mass index (BMI) in pwCF (Lanng 1994), and most recently, a link to the quality of diabetes management has been reported (Moheet 2017). These findings have important implications, as end-stage lung disease is the ultimate event leading to mortality in nearly all pwCF, and the added complication of diabetes may hasten this process, as well as the additional impacts on secondary disease processes as a consequence of improved survival of pwCF. A recent European study places the potential development of these complications for pwCF into a more realistic perspective in their multicenter observational findings that many people with CFRD remain untreated due to resistance of patient acceptance to current practice guideline recommendations (Ballmann 2018a).

Description of the intervention

The Cystic Fibrosis Foundation (CFF) guidelines recommend insulin as the treatment of choice, based on evidence supported by observation of increasing trends toward insulin deficiency over time (Moran 1991; Moran 2010); however, insulin deficiency is seldom absolute, as ketoacidosis is a very uncommon complication in CF. Increasing insulin resistance has further been correlated to the progressive development of impaired glucose tolerance seen in CF (Hardin 1997). The implication of both a relative decrease in pancreatic insulin release, and an increase in insulin resistance to glucose metabolism by the body suggests potential roles for oral insulin-releasing hypoglycemic medications and the newer classes of injectable and oral insulin-sensitizing medications (which influence the role of the hormone incretin in enhancing insulin action) and sodium-glucose cotransporter-2 (SGLT2) inhibitors that block glucose uptake in the kidney as potential additional agents for use in the management of CFRD insulin therapy.

Insulin used to treat people with diabetes is manufactured either by genetic engineering or by chemical manipulation, or a combination of both, to create synthetic variants of human insulin, each manipulation causing changes in insulin rate of absorption, onset and duration of action. Insulin is typically injected, usually just under the skin or in the case of insulin pumps, through a catheter just below the skin. Insulin can also be delivered in the hospital setting though direct infusion into a vein.

Alternatives to insulin are as follows.

- Oral hypoglycemic medications to increase insulin secretion in individuals still able to produce insulin, such as slower-acting sulfonylureas and more rapid acting meglitinides, are typically taken with meals and given once or twice daily depending on their duration of action.
- Bigunides - the only drug of this class currently available is metformin, which is given as an oral dose once to three times daily.
- Glitazones are taken orally, with pioglitazone taken once daily not in association with meals.
- Medications impacting incretin (a hormone that regulates the body's own insulin release and slows the body's ability to absorb glucose) for individuals still able to produce insulin, such as the liptin class of drugs (dipeptidyl-peptidase 4 inhibitors) given orally, once or twice daily, depending on the brand used, with or without meals; and synthetic incretin given as subcutaneous injections once a week and not associated with meals.
- SGLT2 inhibitors given once daily as an oral medication.

How the intervention might work

Therapeutic reports for CFRD which have discussed the impact on pulmonary function and body weight (as a proportion to the square of the height known as the BMI) have been limited to individuals managed by insulin therapy. The institution of insulin therapy aimed toward optimizing glycemic control to the range recommended by the ADA (ADA 2004) has been recently demonstrated to have a positive impact toward improving glycemic control based on HbA1c measurements and to minimize long-term microvascular disease based on correlations from a recent prognostic cohort study (Schwarzenberg 2007). The effect of maintaining HbA1c at or below 7% in CFRD is now significantly associated with minimizing the complications of diabetes on microvascular disease at a prevalence even more reduced than is seen for type 1 and type 2 diabetes.

The specific actions of the intervention classes listed above are as follows.

- Insulin acts through a tyrosine kinase receptor protein on insulin-responsive cells. Once bound, insulin uses a phosphorylation reaction to activate a sequence of intracellular reactions that ultimately insert a glucose transport protein (GLUTE4 in fat and muscle) into the cell membrane, thereby allowing glucose to enter the cell for metabolic utilization.
- Oral hypoglycemic medications - the slower-acting sulfonylureas and more rapid acting meglitinides work by increasing insulin secretion in individuals still able to produce insulin by closing ATP-sensitive K-channels in the insulin-secreting beta-cell plasma membrane within the pancreas,

which initiates a chain of events resulting in the release of insulin.

- Bigunides, work by reducing liver glucose production; however, in addition these drugs have an anti-inflammatory effect that may be beneficial toward the glucose resistance seen in chronic inflammatory conditions, such as CF.
- Glitazone class of drugs, including glitazone and pioglitazone, enhance insulin sensitivity and also have anti-inflammatory actions. Pioglitazone has not been shown to have the cardiovascular risk of earlier glitazones, and a recent meta-analysis has shown there is no increased risk of bladder cancer associated with its use (Filipova 2017).
- Medications impacting incretin (glucagon-like peptide-1 (GLP-1)) - there are currently two classes of medications that impact on the action of this hormone which is secreted by the gut and regulates the body's own insulin release and as well as slowing the body's ability to absorb glucose. The liptin class of drugs (dipeptidyl-peptidase 4 inhibitors) slows the inactivation of incretin, thereby increasing its concentration and assisting in increasing insulin release. The second class of drugs acts as a synthetic form of incretin.
- SGLT2 inhibitors inhibit glucose absorption from the kidney.

Why it is important to do this review

The CFF guidelines only recommend insulin for treating CFRD (Moran 2010), but a recent multicenter European study indicated that this may lead to a significant number of people with CFRD being undertreated or refusing insulin therapy (Ballmann 2018a). The mechanistic potential of utilizing additional agents other than insulin to manage CFRD, reflects a missed opportunity in effectively managing diabetes in pwCF. Reports of the use of oral hypoglycemic agents for controlling HbA1c are limited. There is only one case-based published study reporting the effects of insulin-sensitizing agents (Onady 2006). Recommendations for glycemic control by the ADA emphasize the importance of optimizing the secondary prevention of the complication of microvascular disease in type 1 and type 2 diabetes, but there is still uncertainty as to how this control impacts on microvascular disease in CFRD, pulmonary function or optimal weight through improved carbohydrate metabolism (ADA 2004).

This version of the review is an update of previous versions (Onady 2005; Onady 2013; Onady 2016).

OBJECTIVES

To establish the effectiveness of drugs (injectable and oral agents) for managing diabetes in people with cystic fibrosis (pwCF) in relation to blood sugar levels, lung function and weight management.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Participants of all ages established as having CF, as determined by a positive diagnostic test for CF that may include sweat, nasal epithelial and genotype testing associated with pulmonary or gastrointestinal disease or both. Diabetes from this cohort will be further established by oral glucose tolerance testing, A1C data, two fasting or random blood sugars as defined by ADA standards (ADA 2004). The CFF Guidelines (USA) related to a diagnosis during pulmonary exacerbations and in those with CF requiring feeding tubes may also be additionally used in establishing diagnostic criteria for CFRD.

Types of interventions

We aimed to compare different insulin regimens, either alone or in conjunction with additional oral or injectable diabetic medications, to regimens of oral diabetic medications to injectable diabetic medications (post hoc change). In a further post hoc change, we planned to compare injectable medications to placebo, insulin or oral medications. We originally did not plan to include trials comparing an active treatment-only regimen with a placebo arm, as we thought therapy for diabetes was unlikely to be withheld on ethical grounds; however, we did identify such trials and included them (post hoc change).

Insulin preparations

1. short-acting insulin, with duration of action typically lasting two to four hours
2. intermediate-acting insulin, with duration of action typically to 12 hours
3. long-acting insulin, with duration of actions approaching 24 hours

Oral agents (split by class in a post hoc change)

1. sulphonyureas and related agents
2. biguanides and related agents
3. glitazones and related agents
4. other agents that specifically manage hyperglycemia, such as dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

Injectable agents (post hoc addition)

1. incretin-based therapy including GLP-1 receptor agonists

Types of outcome measures

Primary outcomes

1. Biochemical measures of glycemic control, i.e. HbA1c, fasting and two-hour post-meal serum blood sugar values
2. Pulmonary function (absolute values and change from baseline)
   a. forced expiratory volume (FEV_1) (% predicted and L)
   b. forced vital capacity (FVC) (% predicted and L)
3. Assessment of nutritional status (e.g. body mass index (BMI))

Secondary outcomes

1. Prevalence of microvascular and macrovascular disease
   a. retinopathy
   b. neuropathy
   c. nephropathy
2. Rate of pulmonary exacerbations (post hoc change)

3. Complications of therapeutic management
   a. hypoglycemia (specifically related to oral hypoglycemic and insulin agents)
   b. liver toxicity (specifically related to the thiazolidinedione class)
   c. metabolic effects on acid-base status (specifically related to biguanides (metformin))
4. Clinical status (post hoc change)
   a. six-minute walk test
   b. health-related quality of life (HRQoL) instrument (e.g. the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009))
   c. mortality

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

Relevant trials were sought from the Group's Cystic Fibrosis Trials Register using the terms: insulin OR diabetes.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the *Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Group's CF Trials Register: 10 September 2020.

We also searched the following databases and registries:

- PubMed (https://www.ncbi.nlm.nih.gov/pubmed/;1946 to 21 March 2020);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 21 March 2020);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; attempted search 17 May 2020, but the site was not available to search due to Covid-19).

For details of our search strategies, please see Appendix 1.

Searching other resources

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials. We also handsearched abstracts from pulmonary and North American Cystic Fibrosis Conference symposia from 2004 up to 2018.

Data collection and analysis

Selection of studies

Two authors independently selected trials to be included in the review. No disagreement occurred between the authors, but if in future these do occur the authors will resolve these by discussion.

Data extraction and management

Each author independently extracted data using standard data acquisition forms; however, the authors judged the data from one of the included cross-over trials to have been more appropriately analysed in the original paper and since they were not able to obtain first-arm data from the trial investigators, they have reported results narratively directly from the publication (Moran 2001). If it is necessary for future updates of the review, the review authors will request individual or additional summary data from the trial authors.

The authors have presented the different classes of agents in separate comparisons.

The authors planned to measure outcome data at 1, 3, 6, 12 months and annually thereafter. They were able to report data for glucose levels, weight, fat mass and lean mass and hypoglycemic events at three months and for BMI, FEV_1 and FVC at 12 months. If, for future updates, trial investigators report any other relevant time points, then the review authors will give consideration to these too.

For any data presented as means and standard errors (SEs) in the cross-over trial by Grover and the parallel trial by Moran (Grover 2008; Moran 2009), the review authors converted the SEs to standard deviations (SDs) to allow the to enter data in the analysis. They did not combine data from the cross-over trial with any data from the parallel trial.

Assessment of risk of bias in included studies

In order to establish a risk of bias for the included trials, for the original review each author assessed the methodological quality of the trial. In future, authors will also monitor the consistency of inclusion and exclusion criteria, the appropriateness of comparisons and the rate of attrition.

For the updates from 2013 onwards, the authors assessed the risk of bias of the included trials according to the methods recommended by Cochrane (Higgins 2011). These methods examine internal validity by addressing selection, performance and attrition bias. Authors also assessed concealment of treatment allocation using this methodology. Authors prioritized external validity to assure the availability of adequate information regarding the characteristics of participants and their results in the included trials. Authors also compared the outcomes listed in the methods section of the trial publication to the results reported to assess for selective outcome reporting. For each included trial, the authors gave a judgement of low, high or unclear risk of bias for each of the criteria examined.

Measures of treatment effect

In future updates of this review, for binary outcomes the authors plan to calculate a pooled estimate of treatment effect for each outcome across trials using the risk ratios (RRs) and their 95% confidence intervals (CIs).

For continuous outcomes, the authors measured the mean change from baseline for each group or mean post-treatment or post-intervention values and SD for each group. Where it was necessary, they calculated the SD from the SE which was presented in the trial publication. The authors used a pooled estimate of treatment effect by calculating the mean difference (MD) with 95% CIs.

Unit of analysis issues

Cross-over trials may be relevant when both insulin and oral agents are involved and indeed two of the included trials were of crossover design (Grover 2008; Moran 2001). The authors treated the data from the Grover trial as if it had been a parallel trial since the first-arm trial data were not available as confirmed by the trial authors (Grover 2008). No first-arm data were available for analysis from the Moran trial despite the review authors contacting the trial authors for more information, and on previous advice from a statistician the results from this trial, which were analysed more appropriately in the original trial publication, are reported in the review narratively (Moran 2001). The authors did not combine data from the cross-over trial with those from the parallel trial. If, in the future, the authors include further cross-over trials, they will decide whether to report these results narratively also, or they may decide to analyse the cross-over trials as if they had been parallel trials (assuming a correlation of zero as the most conservative estimate). Elbourne says that this approach produces conservative results as it does not take into account within-patient correlation. Also each participant appears in both the treatment and control group, so the two groups are not independent (Elbourne 2002).

Dealing with missing data

For the current version of the review, the authors have presented the data which are reported in the trial publications. They have tried to obtain first-arm data from the authors of two trials, but the investigators informed the review authors that it was not possible to provide these data as they were no longer available (Grover 2008; Moran 2001). In future updates of this review, the authors will seek data on the number of participants with each outcome measure by allocated treated group, irrespective of compliance or otherwise excluded from treatment at follow up. If these data are not available in publications, the authors will make every attempt to contact the trial investigators for further information.

Assessment of heterogeneity

When the authors are able to include a sufficient number of trials in the review, they will test for heterogeneity between trial results using a standard Chi^2 test and the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across trials that are due to heterogeneity rather than by chance. The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003).

Data synthesis

The authors have analysed data using the fixed-effect model and will continue to do so for future updates, unless additional data result in statistical heterogeneity (I^2 value of over 50%) in which case they will use a random-effects model when combining data from trials.

Subgroup analysis and investigation of heterogeneity

In future, if sufficient trials (n = 10) are included and there is significant heterogeneity between the trials, the authors plan to perform subgroup analyses investigating:

- age (pediatric versus adult participants (0 to 18 years versus over 18 years of age);
- severity of baseline pulmonary function with mild disease (down to an FEV_1 of 80% predicted), moderate disease (between 80% and 40% predicted) and severe disease (less than 40% predicted);
- stratification of various levels glycemic control as identified through HbA1c with adequate control at less than 7%, intermediate control between 7% to 8% and in poor control greater than 8%.

'End-of-life' onset of diabetes may imply a different quality of diabetic control than for the younger diabetic identified earlier and with a milder baseline chronic pulmonary disease setting.

Sensitivity analysis

When we are able to include sufficient trials we plan to perform a sensitivity analysis based on the potential diversity in trial parameters. As an example, many trials from North America omit correlations of diabetic control to HbA1c; whereas European trials tend to follow this closely. Plotting effect estimates against risk of bias measures or performing cumulative meta-analysis based on quality order may also be effective at addressing problems surrounding composite scales.

Summary of findings tables

We constructed a summary of findings table for each comparison in the review and presented results for the following outcomes at six months:

1. HbA1c;
2. FEV_1 (% predicted) change from baseline;
3. FVC (% predicted) change from baseline;
4. BMI;
5. hypoglycemia.

We used the GRADE approach, described in Chapter 12 of *the Cochrane Handbook of Systematic Review for Interventions* (Schünemann 2011) to classify the body of evidence for each outcome as high, moderate, low or very low. The quality of the evidence was downgraded across five domains; risk of bias, indirectness, inconsistency, imprecision and publication bias. Where there was serious risk of bias we downgraded by one level and where it was very serious we downgraded it by two levels. Where we judged the evidence not to be high quality, we described the rationale for this judgement in footnotes to the table.

RESULTS

Description of studies

Results of the search

The searches identified 29 trials (46 references). Four trials are included in the review, 22 trials were excluded and one trial is as yet only available as an abstract and is listed as 'Awaiting classification'

until the full paper is published (de Lind 2014). Two trials are listed as ongoing (NCT01851694; NCT02202876).

Included studies

Four trials (nine references) were included in this review (Ballmann 2018b; Grover 2008; Moran 2001; Moran 2009).

Trial Design

Two trials were of cross-over design (Grover 2008; Moran 2001) and two were of parallel design (Ballmann 2018b; Moran 2009). Both cross-over trials included a washout period. Grover used used a one-month washout period (Grover 2008) and Moran utilized three separate single doses of different interventions over a one-month to two-month period (Moran 2001). The later Moran trial also compared three interventions but in a parallel design (Moran 2009). Duration of the trials ranged from a single-dose trial (Moran 2001) to 24 months (Ballmann 2018b). Two included trials were multicenter; one was undertaken in 14 centers in the USA, Canada and the UK (Moran 2009) and the second was undertaken in 49 centers across Austria, France, Germany and Italy (Ballmann 2018b).

Participants

The number of participants enrolled in the trials ranged from seven (Moran 2001) to 100 (Moran 2009). However, the proportion of withdrawals ranged from 0% (Moran 2001) to 27% (Moran 2009) and of the participants in the later Moran trial, 20 were diagnosed with impaired glucose tolerance (IGT) and not CFRD meaning the number of participants for whom data are available ranges from seven (Moran 2001) to 67 participants (Ballmann 2018b). In all four included trials there were roughly equal numbers of male and female participants enrolled overall. The mean (SD) age ranged from 22 (8.9) years (Ballmann 2018b) to 34 (8) years (Grover 2008). All trials stated that participants were clinically well and two trials required that participants had not experienced acute illness in the previous two (Moran 2009) or three months (Moran 2001).

Interventions

The four included trials employed different interventions (Ballmann 2018b; Grover 2008; Moran 2001; Moran 2009).

Insulin versus control

Two three-arm trials by Moran compared insulin to control (Moran 2001; Moran 2009). The earlier trial compared single-dose treatment of insulin (0.1 unit/kg) administered 10 minutes prior to a meal to no medication (Moran 2001), while the later trial compared insulin (0.5 unit insulin aspart/15 g dietary carbohydrate) to placebo three times daily before meals (time frame not stated) (Moran 2009).

Repaglinide versus control

Both Moran trials also compared repaglinide to control (Moran 2001; Moran 2009). The earlier trial compared single-dose treatment of repaglinide (1 mg) administered 10 minutes prior to a meal to no medication (Moran 2001), while the later trial compared 2 mg repaglinide to placebo three times daily before meals (time frame not stated) (Moran 2009). In this second trial by Moran, 17% of participants had doses of repaglinide reduced due to hypoglycemia (Moran 2009).

Insulin versus repaglinide

Three trials compared insulin with oral repaglinide (Ballmann 2018b; Moran 2001; Moran 2009). Ballmann compared insulin, with doses starting at 0.05 units/kg body weight and then adjusted to maintain a post-prandial glucose over 160 mg/dL, to oral repaglinide, with doses ranging from 0.5 mg to 12 mg/dL again adjusted to keep postprandial glucose at over 160 mg/dl (Ballmann 2018b). The earlier Moran trial compared single-dose treatments of insulin (0.1 unit/kg) versus repaglinide (1 mg); both insulin and repaglinide were administered 10 minutes prior to a meal (Moran 2001). The later Moran trial compared insulin (0.5 unit insulin aspart/15 g dietary carbohydrate) to repaglinide (2 mg) three times daily before meals (time frame not stated) (Moran 2009). In this second trial by Moran, 17% of participants had doses of repaglinide reduced due to hypoglycemia (Moran 2009).

Neutral protamine Hagedorn (NPH) insulin versus glargine

The trial comparing neutral protamine Hagedorn (NPH) insulin to glargine administered both treatments once daily at bedtime (Grover 2008). The average total daily insulin dose observed was 0.7 units/kg/day for each insulin, with mean (SD) insulin to carbohydrate ratios of 1.5 (0.2) NPH and 1.3 (0.1) glargine aspart/15 g carbohydrate, P = 0.05. The mean (SD) dose of glargine was 46 (4)% and of NPH 38 (3)% of the total daily insulin dose (Grover 2008).

Outcome measures

Three of the four trials reported on blood glucose levels and adverse events (Grover 2008; Moran 2001; Moran 2009). The two longer trials also reported quality of life (QoL) along with measures of nutritional status including body mass index (BMI), weight, fat and lean mass (Grover 2008; Moran 2009). The second Moran trial reported on lung function and National Institute for Health (NIH) prognostic score (Moran 2009). While the fourth, and most recent, trial did not report hypoglycemic events, the authors did report on FEV_1 and BMI z scores, glycaemic control (mean change in HbA 1c), and adverse events (pulmonary events and pulmonary events leading to hospital admission) (Ballmann 2018b).

Excluded studies

We excluded 22 trials (34 references) identified in the searches. Of these, 13 were not randomized controlled trials (Borowitz 2005; Chernoff 2002; Franzese 2005; Hardin 2009; König 2005; Mahroukh 2005; Marshall 2005; Milla 2005; Onady 2006; Peraldo 1998; Reali 2006; Sulli 2007; Ward 1999). One trial was of type 1 diabetes not CFRD (Teeter 2004); three trials included participants with glucose intolerance and not CFRD (Geyer 2019; Minicucci 2012; NCT01149005) and one participants who were pre-diabetic (NCT02496780); one trial was of interventions to promote treatment adherence in children with type 1 diabetes or CF and not a comparison of treatments for CFRD (Driscoll 2009). A short-term comparison of a non-pharmacological approach (exercise) to controlling glucose in people with CF (Beaudoin 2015) did not include an intervention used in this review. Two additional studies reported on glucose trends in pwCF but no CFRD, one in a group that were pancreatic insufficient (Eiel 2018) and another only followed during pulmonary exacerbation (Sc 2010); these were excluded as they did not meet inclusion criteria for this review.

Studies awaiting classification

We have listed one trial as 'Awaiting classification' as it is currently only available as a single abstract (de Lind 2014). The trial is a randomized, triple-blind cross-over trial comparing insulin therapy plus metformin to placebo. It consists of two three-month therapy periods separated by a four-week washout period. The trial recruited 17 adults with CF, of whom 14 have completed the trial. Outcomes measured include insulin need, HbA1c levels and glucose levels (de Lind 2014).

Ongoing studies

Two trials are listed as ongoing (NCT01851694; NCT02202876).

The mechanistic study may not be eligible for inclusion in this review as the outcome is to detail the insulin response in CF to incretin stimulus to the pancreas (NCT01851694). Their outcomes, if resulting in a significant insulin response, would support the need for more relevant clinical trials following the glycemic outcomes more relevant to this review. The mechanistic study looking at redox effects in CFRD will monitor cysteine/cysteine ratio response to performing the oral glucose tolerance test, versus a meal (NCT02202876). These outcomes will yield minimal clinical relevance to supporting the treatment options of interest for this review.

Risk of bias in included studies

Allocation

Generation of randomization sequence

Two trials were judged to have an unclear risk of bias for sequence generation (Grover 2008; Moran 2001). Grover did not provide details of the randomization sequence, but made a statement that groups were similar in demographic characteristics and gender proportion, although a table of baseline comparisons was not provided (Grover 2008). In the earlier trial, Moran does state that the interventions were given in random order, but does not describe how this order was generated (Moran 2001).

We judged the remaining two trials to have a low risk of bias from the generation of the randomization sequence (Ballmann 2018b; Moran 2009). The randomization list in the Ballmann trial was generated by a geigy random number table and stratified by gender and age (10 to 15 years and over 15 years of age) (Ballmann 2018b). Moran stated that stated that block randomization using a pseudo-random number generator with stratification by center was employed (Moran 2009).

Concealment of allocation

Three trials were judged to have an unclear risk of bias for allocation concealment as they did not provide any details in their respective publications (Grover 2008; Moran 2001; Moran 2009).

We judged one trial to have a low risk of bias from allocation concealment as participants and clinicians were informed of randomization by a central fax (Ballmann 2018b).

Blinding

We estimate the risk of bias from blinding as high in three trials (Ballmann 2018b; Grover 2008; Moran 2001). The participants in the Ballmann trial either received insulin via a syringe or oral repaglinide (Ballmann 2018b). The Grover article states that this was a cross-over trial, so that once randomized to start either therapy (bedtime NPH- Aspart OR bedtime glargine) the participant (and physician) would be aware of the treatment given due to the frequency of dosing (Grover 2008). The earlier Moran paper does not discuss blinding of participants, clinicians or outcome assessors, however, as the interventions were either no medication, insulin via a syringe or oral repaglinide it would have been impossible to blind the participants or the clinicians to the treatment group (Moran 2001).

In the later Moran trial, participants were blinded when receiving either the oral agent or the oral placebo, which leads to a low risk of bias (Moran 2009). However, it should be noted that it was not possible to blind participants receiving insulin, so this arm of the trial is at risk of bias from blinding (Moran 2009).

Incomplete outcome data

We judged two trials to be at high risk of bias from incomplete outcome data (Ballmann 2018b; Moran 2001). For the Ballmann trial, 75 participants were initially randomised (34 to receive repaglinide and 41 to receive insulin), but four participants did not commence treatment leaving 71 participants in the trial (33 in the repaglinide group and 38 in the insulin group). Of these, three participants from the repaglinide arm and one participant from the insulin arm were not included due to no recording of HbA1c after the baseline reading, so 67 participants were included in the analysis (30 in the repaglinide group and 37 in the insulin group). In addition, missing data at defined times were imputed with available measurements before and after the missing visit (Ballmann 2018b). In the Moran trial, while there was no attrition over this brief five-hour period, the paper stated outcomes were measured at 20-minute intervals, but only presented data for two and five-hour time points (Moran 2001).

We judged one trial to have an unclear risk of bias (Grover 2008). The Grover trial reported that one male participant dropped out of the group who received NPH first, however, no reason was given for this and it was also not stated in which arm of the trial the dropout occurred (Grover 2008).

We judged one trial to have a low risk of bias (Moran 2009). All individuals dropping out from this trial were detailed and there were no significant differences in baseline characteristics for individuals dropping out, with the exception of the CFQOL measure, for which it was noted that those stopping early had lower eating disturbance scores and social or marginalization scales ($P < 0.05$) (Moran 2009).

Selective reporting

We judged three included trials to have a high risk of bias due to selective reporting (Grover 2008; Moran 2001; Moran 2009). Although all four mention all outcomes which are stated in the 'Methods' section in their respective 'Results' sections, they do not always provide data and often there are just statements that there was no difference between treatment groups. We contacted the authors for the data to enter in our analysis, but the data are not available, for this reason we judge there to be a high risk of selective reporting bias.

We judged one trial to have a low risk of bias as all stated outcomes were recorded and reported (Ballmann 2018b).

Other potential sources of bias

We judged the Ballmann trial to have an unclear risk of bias due to industry sponsorship. While this trial was sponsored by Novo Nordisc, they were only one of three sponsors or collaborators and it is not clear how much influence they had over the trial (Ballmann 2018b).

We judged three included trials to be at high risk from other potential sources of bias (Grover 2008; Moran 2001; Moran 2009).

In the Grover trial, diabetic participants with normal fasting blood sugars were excluded from the trial (Grover 2008). The Grover trial was of cross-over design, but we analysed the data as if the trial was of parallel design since first arm data were not available. This approach produces conservative results as it does not take into account within-patient correlation. Also, each participant appears in both the treatment and control group, so the two groups are not independent (Elbourne 2002); hence there is an additional risk of bias to the results.

In the 2001 Moran trial, the insulin doses were chosen at a pharmacological optimal dose range (0.1 unit/kg/body weight); while repaglinide dosing at 1 mg only represents 25% of the recommended maximal dose (Moran 2001).

In the later Moran trial, diabetic participants with fasting hyperglycemia were excluded from the trial. Furthermore, after the trial was started four repaglinide participants (17%) had doses of medication reduced compared to only two insulin-only participants, which could explain the reason the repaglinide lost statistical significance after the first six months of the trial (Moran 2009).

Effects of interventions

See: **Summary of findings 1** Summary of findings: insulin versus placebo for CFRD; **Summary of findings 2** Summary of findings: repaglinide versus placebo for CFRD; **Summary of findings 3** Summary of findings: repaglinide versus insulin for CFRD; **Summary of findings 4** Summary of findings: NPH insulin versus glargine for CFRD

In the section below only those comparisons and outcomes for which information or data are available are presented. Data from the cross-over trials were not combined with those from the parallel trials. The effects of interventions are summarised in the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Insulin versus control

Two trials (n = 68) presented results for this comparison (Moran 2001; Moran 2009), but we were only able to enter data in the graphs for the placebo-controlled trial (n = 61 for three arms, n = 39 for this comparison) (Moran 2009). We have presented the results from the earlier trial comparing insulin to no treatment narratively. A summary of these findings is presented in the tables (Summary of findings 1).

Primary outcomes

1. Biochemical measures of glycemic control

In the comparison of insulin lispro versus placebo the earlier Moran trial reported that there was a benefit seen glucose AUC (reduction) at both the two-hour time point ($P < 0.05$) and the five-hour time point ($P < 0.05$) (Moran 2001). Peak insulin levels fur AUCs were not measured in the later Moran trial (Moran 2009).

Specific data were not reported, but the authors commented that postprandial glucose in participants receiving insulin therapy did not achieve statistical significance, and that HbA1C levels did not significantly change in either this group of participants or those on placebo (Moran 2009) (very low-quality evidence).

2. Pulmonary function

The earlier Moran trial did not report on this outcome (Moran 2001).

In the later trial, Moran reported data for change in FEV_1 (% predicted) and FVC (% predicted) at 12 months (Moran 2009). There were no statistically significant differences detected in treatment groups between insulin compared to placebo for CFRD participants; for FEV_1, MD 1.20 (95% CI -5.63 to 8.03) (Analysis 1.1) and for FVC, MD 0.60 (95% CI -5.67 to 6.87) (Analysis 1.2) (both low-quality evidence).

3. Assessment of nutritional status

The later Moran trial reported on this outcome (Moran 2009) and demonstrated a mean change in BMI at 12 months for insulin of 0.39 compared to placebo of -0.02, resulting in a non-significant MD of 0.41 (95% CI -0.23 to 1.05) (Analysis 1.3) (low-quality evidence).

Secondary Outcomes

2. Prevalence of secondary infection complications

The 2001 trial did not report on this outcome (Moran 2001). While the later trial did not specifically report these data, the authors commented that there were no differences in the number of episodes of acute illness during the year of study in either the insulin or placebo arms (Moran 2009).

3. Complications of therapeutic management

a. hypoglycemia (specifically related to oral hypoglycemic and insulin agents)

In the earlier trial, the investigators reported two incidences of hypoglycemia (glucose level 48 to 54 mg/dl, 2.7 to 3.0 mmol/l) after receiving insulin and one after the test meal with no medication. In all cases catecholamine-related symptoms were present but easily tolerated. These episodes occurred on average four hours after the test meal and resolved spontaneously without glucose administration after 10 to 15 minutes (Moran 2001). When entered in the graphs, these data did not give a significant result, RR 2.00 (95% CI 0.23 to 17.34) (Analysis 1.4).

In the later trial, no serious episode of hypoglycemia was recorded, but in the first three months mild hypoglycemic events were reported in 16% of insulin participants and none receiving placebo ($P < 0.04$). When entered into the graphs these data did not give a significant result, RR 9.23 (95% CI 0.53 to 159.14) (Analysis 1.4) (low-quality evidence). However, caution is advised on interpreting these results since Moran does not provide information as to whether these events occurred in those with CFRD or those with

impaired glucose tolerance (IGT). After this time point, there were no significant differences between groups in the frequency of hypoglycemia, and some participants in the placebo group reported episodes of mild hypoglycemia (Moran 2009).

4. Clinical status

b. HRQoL

Specific data were not included for insulin-treated participants from either trial (Moran 2001; Moran 2009); however, the 2009 trial report did state that CFQOL scores did not differ between insulin or placebo groups at baseline or between these groups at the end of the treatment year (Moran 2009).

c. Mortality

Mortality was not specifically reported for either trial, but details of participants leaving the trial were recorded and none from insulin, repaglinide nor the placebo groups were excluded as a result of mortality (Moran 2009).

Repaglinide versus control

Two trials reported on this comparison (n = 45) (Moran 2001; Moran 2009) and a summary of the evidence is presented in the tables (Summary of findings 2).

Primary outcomes

1. Biochemical measures of glycemic control

Both trials only reported this outcome narratively (without actual data) (Moran 2001; Moran 2009). In the earlier trial (n = 7), for the comparison of repaglinide versus placebo, there was a significant decrease in glucose AUC in the repaglinide group at the five-hour time point (P = 0.03); however, there was no significant benefit found at the two-hour time point (Moran 2001). The later trial reported that HbA1C levels did not significantly change in either the repaglinide and placebo groups (Moran 2009) (very low-quality evidence).

2. Pulmonary function

Moran only reported the change from baseline in FEV_1 (% predicted) and FVC (% predicted) in the later trial (Moran 2009). At 12 months, there were no significant differences between the repaglinide or the placebo groups for either the change in FEV_1 % predicted, MD 1.70 (95% CI -5.13 to 8.53) (Analysis 2.1) or the change in FVC % predicted, MD -1.00 (95% CI -7.40 to 5.40) (Analysis 2.2) (both low-quality evidence).

3. Assessment of nutritional status

Moran reported that repaglinide demonstrated a mean difference for BMI change of 0.15 compared to placebo of -0.02, resulting in a non-significant MD of 0.17 (95% CI -0.47 to 0.81) (Analysis 2.3) (low-quality evidence).

Secondary Outcomes

2. Prevalence of secondary infection complications

The prevalence of secondary infection was not detailed in the included trials, but the authors from the later trial did state that there were no differences in the number of episodes of acute illness during the year of study in either the repaglinide or the placebo arm (Moran 2009).

3. Complications of therapeutic management

a. hypoglycemia (specifically related to oral hypoglycemic and insulin agents)

In the earlier trial, one episode of hypoglycemia (glucose level 48 to 54 mg/dL, 2.7 to 3.0 mmol/L) occurred in each group (Moran 2001). In all cases catecholamine-related symptoms were present but easily tolerated. These episodes occurred on average four hours after the test meal and resolved spontaneously without glucose administration after 10 to 15 minutes (Moran 2001). When analysed, these data showed no difference between groups, RR 1.00 (95% CI 0.08 to 13.02) (Analysis 2.4).

As for the previous comparison, up to three months there were mild hypoglycemic events reported in 23% of repaglinide participants, but no placebo participants reported hypoglycemia (P < 0.04). When entered into the graphs, the result is not significant, RR 12.52 (95% CI 0.74 to 211.20) (Analysis 2.4) (very low-quality evidence). However, caution is advised on interpreting these results since Moran does not provide information as to whether these events occurred in participants with CFRD or participants with IGT. After three months, this difference was no longer detected (Moran 2009).

4. Clinical status

b. HRQoL

Specific data were not presented; however, the authors did state that CFQOL scores did not differ between groups at the end of the treatment year (Moran 2009).

c. mortality

Mortality was not specifically reported for this trial, but participants leaving the trial were detailed and none from the repaglinide group nor the placebo group were excluded as a result of mortality (Moran 2009).

Insulin versus repaglinide

Three trials reported on this comparison (n = 119) (Ballmann 2018b; Moran 2001; Moran 2009) and a summary of the evidence is presented in the tables (Summary of findings 3).

Primary outcomes

1. Biochemical measures of glycemic control

Only one trial reported data for analysis (Ballmann 2018b) and two trials did not report specific data (Moran 2001; Moran 2009).

The more recent trial (n = 67) reported that mean change in HbA1c(%) levels were not significantly different between the repaglinide group and the insulin group after 12 months (Ballmann 2018b), MD -0.30 % (95% CI -0.14 to 0.74) or after two years of intervention, MD 0.40 % (95% CI -0.08 to 0.88) (Analysis 3.1) (high-quality evidence). In the later Moran trial (n = 45), investigators commented that postprandial glucose in participants receiving insulin compared to repaglinide therapy did not achieve statistical significance, and that A1C levels did not significantly changed between these groups of treated participants (Moran 2009).

The earlier Moran trial (n = 7) reported that insulin lispro seemed to have a more beneficial effect than repaglinide on post-meal glucose excursion in CFRD; P < 0.05 when comparing insulin to repaglinide at both two and five hours post-meal (Moran 2001). Investigators reported significant differences between the two drugs in the peak

glucose level (P = 0.02), the two-hour glucose area under the curve (AUC) (P = 0.02), and the five-hour glucose AUC (P = 0.01). The paper also states that at the doses used in the trial, neither insulin lispro or repaglinide significantly changed the peak insulin level or the two-hour insulin AUC compared with baseline (Moran 2001).

2. Pulmonary function

FEV_1

Two trials reported on FEV_1 (% predicted) at 12 months (n = 112) (Ballmann 2018b; Moran 2009), but there was no statistically significant result between groups, MD -0.51 % predicted (95% CI -4.22 to 3.20) (Analysis 3.2) (moderate-quality evidence). Only Ballmann reported this outcome at the two-year time point (n = 67) and again results showed no significant difference between groups, MD -0.10 % predicted (95% CI -4.12 to 3.92) (Analysis 3.2).

FVC

The same two trials reported on FVC (% predicted) (n = 112) (Ballmann 2018b; Moran 2009). The analysis showed a non-significant difference between groups at 12 months (n = 112), MD -1.00 % predicted (95% CI -4.29 to 2.29) (Analysis 3.3) (moderate-quality evidence). Only Ballmann reported this outcome at the two-year time point (n = 67) and again results showed no significant difference between groups, MD -3.40 % predicted (95% CI -7.37 to 0.57) (Analysis 3.3).

3. Assessment of nutritional status

One trial (n = 45) comparing insulin and repaglinide demonstrated a non-significant MD in BMI of 0.24 (95% CI -0.34 to 0.82) (Analysis 3.4) (Moran 2009) (low-quality evidence).

The more recent study reported the change in BMI z score (Ballmann 2018b). The updated analysis (using data from the full paper and not previous abstracts) no longer showed significant improvement in z score in the insulin treatment group compared to repaglinide at 12 months (n = 67), MD 0.00 (95%CI -0.49 to 0.49), and this difference remains non-significant at the two-year point (n = 67), MD 0.40 (95% CI -0.09 to 0.89) (Analysis 3.5).

Secondary Outcomes

2. Prevalence of secondary infection complications

Only one trial reported the prevalence of secondary infection; while this was not detailed, the authors did state that there were no differences in the number of episodes of acute illness during the one-year trial in either treatment arm (Moran 2009).

3. Complications of therapeutic management

a. hypoglycemia (specifically related to oral hypoglycemic and insulin agents)

In the earlier trial, the investigators reported two incidences of hypoglycemia (glucose level 48 to 54 mg/dL, 2.7 to 3.0 mmol/L) after receiving insulin and one after administration of repaglinide. In all cases catecholamine-related symptoms were present but easily tolerated. These episodes occurred on average four hours after the test meal and resolved spontaneously without glucose administration after 10 to 15 minutes (Moran 2001). When entered into the analysis, the result showed no difference between the groups, RR 0.50 (95% CI 0.06 to 4.33) (Analysis 3.6) (low-quality evidence).

The later trial also reported mild hypoglycemic events (Moran 2009). These occurred in 16% of participants in the insulin group and 23% of participants in the repaglinide group at up to three months; after three months, this difference was no longer detected (Moran 2009). Data were analysed in the graphs for the three-month time point and did not give a statistically significant result, RR 1.38 (95% CI 0.48 to 4.01) (Analysis 3.6) (low-quality evidence). No information was available as to whether these participants had CFRD or IGT.

4. Clinical status

b. HRQoL

Only Moran assessed this outcome and specific data were not presented; however, the authors did state that CFQoL scores did not differ between groups at the end of the treatment year (Moran 2009).

c. mortality

Mortality was not specifically reported for either trial, but details of participants leaving the trial were recorded and none from insulin, repaglinide nor the placebo groups were excluded as a result of mortality (Moran 2009).

NPH insulin versus glargine

Only one trial (n = 20) reported on this comparison; the trial was of cross-over design, but we treated it as a parallel trial since data were not available to analyse them correctly (Grover 2008). There was a washout period of one month which separated either 12 weeks receiving NPH at bedtime or 12 weeks receiving glargine at bedtime. A summary of the evidence is presented in the tables (Summary of findings 4).

Primary outcomes

1. Biochemical measures of glycemic control

Results for neither fasting nor two-hour post-prandial glucose values were significant: fasting glucose, MD 10.00 mg/dl (95% CI -12.86 to 32.86); and two-hour post-prandial, MD 8.00 mg/dl (95% CI -10.07 to 26.07) (Analysis 4.1).

3. Assessment of nutritional status

Grover reported a mean change in weight in the glargine group of 1.2 kg compared to a mean change of 0.2 kg in the NPH group resulting in a non-significant MD -1.00 kg (95% CI -2.39 to 0.39) (Analysis 4.2). Grover also assessed both fat mass and lean mass measured by DEXA scans (Grover 2008). Neither outcome was statistically significant: fat mass, MD -0.30 kg (95% CI -1.41 to 0.81) (Analysis 4.3); and lean mass, MD -0.20 kg (95% CI -0.75 to 0.35) (Analysis 4.4).

Secondary Outcomes

2. Prevalence of secondary infection complications

In the short time course of this study, no infectious complications were reported for either group of participants (Grover 2008).

3. Complications of therapeutic management

a. hypoglycemia (specifically related to oral hypoglycemic and insulin agents)

Grover reported the mean number of minor hypoglycemic episodes per participant, but there was no statistically significant difference between the groups, MD -1.00 (95% CI -3.77 to 1.77) (Analysis 4.5) (very low-quality evidence).

4. Clinical status

b. HRQoL

The paper reported that no difference in QoL was observed and that all participants opted to continue treatment with glargine after the trial was completed (Grover 2008).

c. mortality

No mortality was reported for either treatment group; however, there was no reason given for the loss of the participant from the NPH group (Grover 2008).

DISCUSSION

Summary of main results

The prevalence of diabetes in pwCF increases throughout adulthood to rates as high as 50% (Moran 2010), with a 3.6-fold increase in mortality from the additional complication of CFRD in the clinical course of disease (Moheet 2017). The impact of therapy and the extent to which diabetic control can be achieved is just beginning to be addressed.

We have included four trials (n = 145) in this review (Ballmann 2018b; Grover 2008; Moran 2001; Moran 2009). Three of these trials compared insulin to repaglinide (Ballmann 2018b; Moran 2001; Moran 2009); one was a two-arm parallel trial (Ballmann 2018b), whereas the remaining two trials had a third arm of either no medication (Moran 2001) or placebo (Moran 2009). One of these was a short-term RCT (Moran 2001), which has evolved into a three-arm multicenter RCT comparing insulin to repaglinide and placebo over a 12-month period (Moran 2009). The later trial allowed us to generate additional comparisons of insulin versus placebo and repaglinide versus placebo (Moran 2009). The fourth included trial compared NPH insulin and glargine over a three-month period (Grover 2008).

Insulin versus control

One cross-over trial (n = 7) compared insulin to no treatment (Moran 2001) and the three-arm parallel trial (n = 61, n = 39 for this comparison) compared insulin to a placebo (Moran 2009). Only the placebo-controlled trial provided analysable data and reported that A1C levels did not significantly change in the insulin group compared to the placebo group(very low-quality evidence) (Moran 2009). This trial also reported on lung function and nutritional status (BMI) finding no differences between insulin and placebo at 12 months for either of these outcomes (low-quality evidence) (Moran 2009). Neither trial showed any difference in incidences of hypoglycemia (low-quality evidence) (Moran 2001; Moran 2009). The placebo-controlled trial reported no difference in the number of episodes of acute illness or CFQOL scores between groups and while mortality was not specifically reported, no participants were excluded due to mortality (Moran 2009).

Repaglinide versus control

The three-arm parallel trial (n = 61, n = 38 for this comparison) compared repaglinide to placebo (Moran 2009). Investigators found no differences in A1C levels (very low-quality evidence), lung function (low-quality evidence), nutritional status (BMI) (low-quality evidence), the number of episodes of acute illness or hypoglycemia (very low-quality evidence), or in CFQOL scores between groups (Moran 2009). While mortality was not specifically reported, no participants were excluded due to mortality (Moran 2009).

Insulin versus repaglinide

Three trials (n = 119) compared insulin to repaglinide (Ballmann 2018b; Moran 2001; Moran 2009). Data from one parallel trial (n = 67) showed no difference in A1C levels between insulin and repaglinide at either 12 months (high-quality evidence) or at 24 months (Ballmann 2018b). The remaining two trials did not provide analysable data, but the cross-over trial (n = 7) reported that insulin lispro seemed to have a more beneficial effect than repaglinide on post-meal glucose excursion and peak glucose levels at both two and five hours (Moran 2001). The later parallel trial (n = 61, n = 45 for this comparison) did not report any differences in post-prandial glucose or A1C levels between groups (Moran 2009). The two parallel trials (n = 112) found no difference between insulin and repaglinide in lung function (moderate-quality evidence), nutritional status (low-quality evidence), or the number of hypoglycemic episodes (low-quality evidence) (Ballmann 2018b; Moran 2009). Only the later Moran trial (n = 45) reported on secondary infections and CFQOL and found no difference between groups for either outcome (Moran 2009). While mortality was not specifically reported, one trial (n = 45) reported that no participants were excluded due to mortality (Moran 2009).

The later Moran trial identified a slightly more favorable response to insulin and when factoring in the 12-month pre-treatment run-in period the results demonstrated a significant advantage. There were clear differences in the slope of BMI change between the insulin and repaglinide groups during this run-in period. In this review, when factoring out the run-in period which was presented in the original paper, the significance of results vanished and there are no differences between treatment groups (Moran 2009).

NPH insulin versus glargine

One cross-over trial (n = 20) compared receiving NPH at bedtime to receiving glargine at bedtime, with a washout period of one month separating each 12-week treatment arm; however, due to the limited data available we analysed this trial as if it was of parallel design (Grover 2008).

The trial did not report results for HbA1c, but did report no differences between groups in either fasting or two-hour post-prandial glucose values. The trial did not report lung function. In terms of nutritional status, BMI was not reported but there were no differences observed between groups for the change in weight (kg), fat mass (kg) or lean mass (kg). No infectious complications were reported by either group during the trial. There was no difference in the number of minor hypoglycemic episodes per participant between groups (very low-quality evidence); and while there was no difference reported in QoL, all participants opted to continue treatment with glargine after the trial was completed. No mortality was reported for either treatment group; however, there was no

reason given for the loss of the participant from the NPH group (Grover 2008).

The only clear conclusion from the comparison NPH insulin and glargine over a three-month period that we can draw at this time, is that while fasting glucose may be diminished by 2 mg/dL for the long-acting insulin glargine, there is no significant therapeutic advantage in treating people with CFRD and fasting hyperglycemia with glargine insulin compared to protamine-Hagedorn insulin (Grover 2008).

Overall completeness and applicability of evidence

The two Moran trials only investigated a subgroup of people with CFRD with normal fasting glucose values (Moran 2001; Moran 2009). All of the studies reported in this Cochrane Review were focused on adults, so these results cannot be extrapolated to children which would demonstrate an earlier subset of diabetes onset (Ballmann 2018b; Grover 2008; Moran 2001; Moran 2009).

Quality of the evidence

The participant numbers in the trials included in this review were quite small, and the trials were not powered for important clinical outcomes such as FEV_1. In the only trial where powering was adequate for comparisons of BMI, lead-in bias places some concern as to the validity of the reported outcome (Moran 2009). We had hoped to be able to pool data so as to improve on the quality of the currently available evidence, unfortunately there were too many differences between the trials included in the review to allow this, except for one lung function outcome at the 12-month time point (Analysis 3.2).

The quality of the evidence as evaluated by GRADE ranged from very low to high (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4). Reasons for downgrading the quality of the evidence included risks of bias across all domains, but particularly due to concerns surrounding allocation concealment and selective reporting. We also had some concerns due to imprecision from small sample sizes (numbers of participants ranged from seven to 67) and low event rates.

Potential biases in the review process

Any potential bias is limited due to comprehensive searches with no limit on publication status or language, with adherence to Cochrane methodology.

Agreements and disagreements with other studies or reviews

Some CF centers use oral medications to help control diabetes, yet insulin remains the accepted as the treatment or intervention of choice as reported in the CFRD Clinical Practice Guidelines (Moran 2010) and as evident from the interventions investigated in the limited number of trials that have been evaluated for this Cochrane Review. A cohort study has demonstrated the use of insulin in maintaining a HbA1c below 7% and also a significant reduction in microvascular disease for CFRD (Schwarzenberg 2007); however, trials have yet to significantly demonstrate the long-term impact of insulin therapy on lung function. Outcomes reported in the trials included in this review did not demonstrate a significant impact on lung function between the insulins or oral agents identified from the trials. Despite this finding, a single negative outcome trial identified in this current Cochrane Review continues to be cited as a positive trial (Moran 2009) and used to further support insulin-only therapy (Warren 2019). Such reporting needs to be placed in context when considering that a multicenter comprehensive prospective cohort study identifies that only 47% of people diagnosed with CFRD elect to start on insulin therapy, with 41% choosing no therapy (Ballmann 2018a). These authors conclude that the treatment burden of insulin is in part a reason that there is such a low acceptance to initiate therapy for managing diagnosed diabetes and oral hypoglycemic agents, e.g. repaglinide, are already being used as an alternative to insulin to reduce the treatment burden for pwCF diagnosed with diabetes.

Similar to the two Moran trials which only investigated a subgroup of people with CFRD with normal fasting glucose values (Moran 2001; Moran 2009), other non-randomized clinical trials of oral hypoglycemic agents have found that these drugs usually only demonstrate a clinical advantage in this subgroup of people with CF for about the first six months of therapy (Culler 1994; Rosenecker 2001).

With this updated Cochrane Review, we have observed a trend of studies (that are out of the review's scope) but which are beginning to evaluate impaired glucose tolerance with a view to the potential benefits of earlier intervention using long-acting insulin (Pu 2016; Minicucci 2012) or agents impacting incretin mechanisms (Geyer 2019) in the management of these individuals who have a high risk of developing diabetes (Schmid 2014).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no conclusive evidence that any agent (long-acting insulins, short-acting insulins or oral hypoglycemic agents) have a distinct advantage over one another in controlling hyperglycemia or clinical outcomes associated with cystic fibrosis-related diabetes (CFRD). A single-center long term prospective prognostic cohort trial is currently the best evidence available to date that demonstrates that insulin therapy for both normal and elevated fasting hypoglycemia improves the control of microvascular disease in people with CFRD (Schwarzenberg 2007). Outside of this singularly important clinical outcome, the impact on clinical outcomes important to people with cystic fibrosis (pwCF), namely long-term body mass index (BMI) and pulmonary function measures, have yet to be conclusively demonstrated.

Results from this updated Cochrane Review (after factoring out the lead-in bias as noted in the 2010 Moran study) do not allow conclusions to be drawn with regards to the optimal therapy for people with CFRD, despite recommendations in the current version of the CFRD Clinical Practice Guidelines to treat this subgroup of people with CFRD at meal times only with a short-acting insulin (Moran 2010). Contrary to the current CFRD Clinical Practice Guidelines which recommend the use of insulin only for managing CFRD, the results of this Cochrane Review do not show that insulin therapy offers greater clinical benefit compared to the oral hypoglycemic agent repaglinide. However, given the treatment burden which pwCF already bear, treatment with oral agents should be considered for managing CFRD.

Implications for research

Multicenter randomised controlled trials (RCTs) are still required in order to best assess the effectiveness of therapeutic options in the control of CFRD. This Cochrane Review suggests the potential for achieving tighter glycemic control with long-acting insulin for people with CF with fasting hyperglycemia and this could likely be demonstrated in future studies with the use of insulin infusion pumps.

The newer classes of injectable and oral incretin associated therapeutics options have recently demonstrated a beneficial effect in people with CF who are observed to have impaired glucose tolerance (Geyer 2019). There are no trials reported to date, that demonstrate their effectiveness in treating CFRD. This potential class of agents opens up a whole series of therapeutic intervention RCTs to assess their effectiveness compared to insulin, both in their effectiveness in conjunction with insulin compared to insulin alone.

The use of therapeutic agents which may provide additional impact in CF based on the inflammatory effects of insulin sensitivity and the control of levels of inflammatory mediators by mechanisms such as peroxisome proliferator activated receptor gamma (PPARg) receptor agonists still remains to be demonstrated. The concerns with this class of agents are the side effects associated with the glitazones. Cardiac effects associated with the glitazones are less applicable to people with CF, with such a low incidence of coronary artery disease; and osteoporosis concerns may be less problematic in CF due to interleukin inhibitory effect of PPARg agonists on IL-6. Finally, the potential value of metformin in people with CF without hepatic dysfunction demonstrates another potential option in treating CFRD. These additional agents may provide a unique advantage, perhaps as adjuvant therapy to insulin, for a population that is highly adversely impacted by inflammatory disease.

Outcomes of greatest interest in future trials comparing long-acting versus short-acting insulins, or insulins to oral agents and incretin mimics should be powered such that they can include BMI, FEV_1, performance on the six-minute walk test, frequency of hospital admissions and effects on bone metabolism. A further important outcome would be to measure varying adherence rates between insulin therapy and treatment with less burdensome oral agents.

Furthermore, epidemiology demonstrates increased morbidity and mortality for people with CF with glucose intolerance, which prompts RCTs to examine the use of the expanding choices of anti-diabetic agents in the management of pre-diabetics who are screened as glucose intolerant verses conservative observation.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ballmann 2018b

Study characteristics	
Methods	Non-blinded randomized controlled trial. Parallel design. Multicenter: 49 centers in Europe (Austria, France, Germany and Italy). Duration: 24 months.
Participants	75 participants with diabetes confirmed by OGTT enrolled and randomized. Participants excluded if diagnosed with Type I diabetes or with a history of diabetic keto-acidosis.

Ballmann 2018b *(Continued)*

	30/34 participants in the repaglinide group and 37/41 participants in the insulin group included in the analysis (total completing n = 67). Raw data were available for 30 participants in the repaglinide group and 37 in the insulin group at baseline, 26 participants and 34 participants,respectively, after 12 months, and 22 and 23 participants, respectively after 24 months. Changes are calculated from imputed data (missing values imputed with available measurements before and after the missing visit, based on linear interpolation. Age, mean (SD) age: 22.2 (8.9) years. BMI z score, mean (SD): -0.71 (1.1). HbA1C, mean (SD): 6.5 (0.79)%. FEV_1 % predicted, mean (SD): 67.2 (23.2)%.
Interventions	**Group 1**: beginning with 0.05 unit insulin/kg weight injections 3x daily (dose adjustments at 1 week intervals until optimized). **Group 2**: beginning with 0.5 mg repaglinide orally 3x daily (dose adjustments at 1 week intervals until optimized; maximum dose of 12 mg in total split into 3x 4 mg). All interventions were followed over 2 years.
Outcomes	**Primary outcome**: change in HbA1c after 24 months of treatment. **Secondary outcomes**: mean HbA1c and mean blood glucose profile; change in BMI z score; change in FEV_1 % predicted; safety as assessed by antibiotic therapy, adverse events, number of hypoglycemic episodes, all symptomatic hypoglycemia, hypoglycemia needing help of others, hypoglycemia resulting in unconsciousness/coma, number of blood glucose levels below 50 mg/dl.
Notes	Sample size calculation undertaken. Last participant recruited on 01 December 2009. Full analysis of trial data was completed at time of publication. Colloborators: Novo Nordisk A/S; Mucoviscidose-ABCF2; Assistance Publique - Hôpitaux de Paris.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization list was generated by a geigy random number table by central fax randomization. Stratified by gender and age (10 - 15 years and over 15 years of age).
Allocation concealment (selection bias)	Low risk	Central fax randomization.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded and received insulin via a syringe or oral repaglinide. Open-label design to avoid use of double-dummy technique which would have required an unacceptable increase in the number of injections.
Incomplete outcome data (attrition bias) All outcomes	High risk	A modified intention-to-treat analysis was used where participants who received no trial treatments or did not attend follow-up visits were excluded from the analysis. 75 participants were initially randomised (34 to receive repaglinide and 41 to receive insulin). 4 participants did not commence treatment leaving 71 participants in the trial (33 in the repaglinide group and 38 in the insulin group). 3 participants from the repaglinide arm and 1 participant from the insulin arm

Ballmann 2018b *(Continued)*

		were not included due to no recording of HbA1c after the baseline reading was recorded, so 67 participants were included in the analysis (30 in the repaglinide group and 37 in the insulin group). In addition, missing data were imputed with available measurements before and after the missing visit, based on linear interpolation derived from linear regression models with the difference between measurements at 12 and 24 months minus baseline as the dependent variable and treatment group as the categorical independent variable, adjusted for age and sex.
Selective reporting (reporting bias)	Low risk	All outcomes from each group recorded and reported at the conclusion of the trial.
Other bias	Unclear risk	Sponsored by Novo Nordisk A/S - but effects of this are unclear.

Grover 2008

Study characteristics	
Methods	Randomized cross-over trial. Single center: USA. Duration: 12 weeks.
Participants	20 people with CFRD with fasting hyperglycemia only recruited, 1 dropped out (9 men; 10 women). Two groups had similar demographic characteristics and gender split. Age, mean (SD): 34 (8) years. Duration of diabetes, mean (SD): 9 (5) years (diabetes well-controlled).
Interventions	Bedtime NPH insulin versus bedtime insulin glargine. Doses were individually established based on an insulin:carbohydrate ratio and a correction scale; however, the ratio and correction scale ranges within the participant population was not reported in the manuscript. It was noted that the ratio was used to try to maintain target glucose goals between 80-120 mg/dl fasting; 80-150 mg/dl 2 hours after meals.
Outcomes	Total glucose goal of 80 - 120 mg/dL fasting Total glucose goal of 80 - 150 mg/dL 2 hours after a meal Hemoglobin A1c Weight Fat mass (by DEXA) Lean mass (by DEXA) QoL Adverse events
Notes	A 1-month insulin adjustment period was included in the trial during the cross-over period.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of randomization sequence not provided. A statement was made that groups were similar in demographic characteristics and gender proportion, but a table of baseline comparisons was not provided.

Grover 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Concealment of allocation sequence was not discussed in the paper.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded. Article states that this was a cross-over trial so that once randomized to start either therapy wing (bedtime NPH-Aspart OR bedtime glargine) the participant (and physician) would be aware of the treatment given by a factor of the frequency of dosing.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 male dropped out of the group who received NPH first. However, no reason was given or timing of drop out (which arm).
Selective reporting (reporting bias)	High risk	Although all outcomes stated in the methods section are reported in the results section, data are not available for all outcomes for analysis despite contact with the trial authors.
Other bias	High risk	Diabetic patients with normal fasting blood sugars were excluded from the trial. This trial was of cross-over design but we analysed the data as if the trial was of parallel design since first-arm data were not available. This approach produces conservative results as it does not take into account within-patient correlation. Also each participant appears in both the treatment and control group, so the two groups are not independent.

Moran 2001

Study characteristics	
Methods	Randomized cross-over trial. Single center: USA. Duration: 3 separate occasions over 1- to 2-month period.
Participants	7 (3 male, 4 female) participants with routine oral glucose tolerance test in previous 3 months and CFRD without fasting hypoglycemia. Age, mean (SD) age: 24 (5) years. All were chronically infected with CF pathogens, but no acute illness in previous 3 months.
Interventions	3 single-dose treatments over 1 - 2 month period. No medication versus insulin (0.1 unit/kg) 10 minutes pre-meal vs repaglinide (1 mg) 10 minutes pre-meal.
Outcomes	Blood glucose and insulin levels (AUC) at 2 hours and 5 hours post meal, adverse events.
Notes	7 healthy age-, sex- and BMI-matched normal control participants in trial, but data for these not presented.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear, described as treatments given in random order but randomization method not stated.
Allocation concealment (selection bias)	Unclear risk	Not discussed.

Moran 2001 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Participants and clinicians would know whether they were given insulin (syringe) or an oral medication or no medication at the time of the test meal. Blinding of outcome assessors is not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was no attrition over this brief 5-hour trial period. The paper states outcomes measured at 20 minute intervals, but only presents data for 2- and 5-hour time points.
Selective reporting (reporting bias)	High risk	Although all outcomes listed in the methods section appear to be reported in the results section of the paper, data are not available for all outcomes for analysis despite contact with the trial authors.
Other bias	High risk	There is potential bias as to optimization of dosing of agents used in this trial. Insulin doses were chosen at a pharmacological optimal dose range (0.1 unit/kg/body weight); while repaglinide dosing at 1 mg only represents 25% of the recommended maximal dose. Otherwise, control of pre-trial meals, interventions and measurements were identical in each phase of the trial, with the participants serving as their own controls.

Moran 2009

Study characteristics	
Methods	Randomized controlled trial. Parallel design. Multicenter: 14 centers in the USA, Canada and UK. Duration: 12 months. Partially blinded (participants blinded to 2 of the 3 treatment arms).
Participants	100 Tanner 5 participants, without acute infection in 2 months prior to the trial were enrolled. Total cohort: 81 participants (61 CFRD (30 male, 31 female; mean (SD) age 28 (9) years); 20 IGT (15 male, 5 female; mean (SD) age 28 (7) years)). Insulin group: 30 participants (23 CFRD; 7 IGT). Repaglinide group: 26 participants (22 CFRD; 4 IGT). Placebo group: 25 participants (16 CFRD; 9 IGT). A total of 19 participants dropped out or stopped early (51% female; 49% male) representing 80% of participants completing the trial (6 (23%) dropped out from IGT and 13 (18%) from CFRD FH- group) which breaks down to 8 in the insulin group, 6 in the repaglinide group and 5 in the placebo group. Reasons given were as follows: 5 participants dropped out after becoming positive for fasting hyperglycemia (2 in insulin group; 0 from the repaglinide group; 3 in the placebo group); another 6 discontinued for other medical reasons (1 in the insulin group; 4 in the repaglinide group; 1 in the placebo group); and 8 were non-compliant/quit (5 in the insulin group; 2 in the repaglinide group; 1 in the placebo group).
Interventions	0.5 unit insulin aspart/15 g dietary carbohydrate 3x daily. 2.0 mg repaglinide orally 3x daily (17% had doses reduced due to hypoglycemia). Placebo orally 3x daily. All interventions were followed over 1 year.

Moran 2009 *(Continued)*

Outcomes	BMI Pulmonary function Body composition by DEXA CF QoL survey NIH prognostic score Hemoglobin A1c Adverse events
Notes	Repaglinide dosing chosen is mid-range and not optimized to maximum dose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states block randomization using a pseudo-random number generator with stratification by center was used. One third of participants per block were assigned to each treatment arm (page 1784).
Allocation concealment (selection bias)	Unclear risk	Was not detailed in the trial report.
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was done for participants receiving oral agent or oral placebo; not for those receiving insulin.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individuals dropping out from the trial were detailed. No significant differences in baseline characteristics were evaluated for individuals dropping out, with the exception of the CF QoL measure noting those stopping early had lower eating disturbance scores and social/marginalization scales ($P < 0.05$).
Selective reporting (reporting bias)	High risk	Although all outcomes were reported and mostly tabulated by diagnosis, all comparing insulin, repaglinide and placebo, data are not available for all outcomes for analysis despite contact with the trial authors.
Other bias	High risk	Diabetic patients with fasting hyperglycemia were excluded from the trial. Twice as many repaglinide participants (4 or 17%) had doses of medication reduced; compared to 2 on insulin only after the trial was started which could explain the reason the repaglinide lost statistical significance after the first 6 months of the study.

BMI: body mass index
CF: cystic fibrosis
CFRD: cystic fibrosis-related diabetes
DEXA: dual energy X-ray absorption
FH-: without fasting hyperglycemia
IGT: impaired glucose tolerance
NIH: National Institutes of Health
NPH: Neutral Protamine Hagedorn
QoL: quality of life
SD: standard deviation
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beaudoin 2015	A short-term comparison of a non-pharmacological approach (exercise) to controlling glucose in people with CF.
Borowitz 2005	A subset of entire cohort were randomized for pancreatic enzymes, not for diabetic medications. Diabetic outcomes not reported.
Chernoff 2002	Participants with diabetes did not have CF and participants with CF did not have diabetes.
Driscoll 2009	Intervention was to promote treatment adherence in children with Type 1 diabetes or CF and not a comparison of treatments for CFRD.
Eiel 2018	Reported on glucose trends in people with CF who were pancreatic insufficient but did not have CFRD.
Franzese 2005	Not a RCT.
Geyer 2019	A trial of people with glucose intolerance and not CFRD.
Hardin 2009	Cohort study, not a RCT.
König 2005	Not a RCT.
Mahroukh 2005	Not a RCT.
Marshall 2005	Not a RCT.
Milla 2005	Not a RCT.
Minicucci 2012	A trial of people with glucose intolerance and not CFRD.
NCT01149005	Participants do not have CFRD so do not meet review's inclusion criteria.
NCT02496780	Trial looking at insulin effects on protein turn over for pre-diabetic people with CF.
Onady 2006	Not a RCT.
Peraldo 1998	Non-randomized biochemical metabolic trial, longitudinal data analysis.
Reali 2006	Not a RCT, study of a single participant.
Sc 2010	Trial reported on glucose trends in people with CF who did not have CFRD during a pulmonary exacerbation.
Sulli 2007	Not a RCT, 3 case studies.
Teeter 2004	Trial of Type 1 diabetes not CFRD, participants with active lung disease excluded, participants with abnormal pulmonary function at screening excluded.
Ward 1999	Not a RCT. Treatment of participants with CFRD not detailed, longitudinal data analysis.

CF: cystic fibrosis
CFRD: cystic fibrosis-related diabetes
RCT: randomized controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

de Lind 2014

Methods	Randomized, triple-blind, placebo-controlled cross-over trial. Duration: 3 months in first treatment arm, followed by 4-week washout period and then a second 3-month therapy period.
Participants	17 adults with CF randomized; 14 adults completed trial.
Interventions	Treatment: insulin therapy plus metformin. Control: insulin therapy plus placebo.
Outcomes	Insulin need, blood HbA1c levels, glucose levels.
Notes	Published as abstract only and with limited results. Await full publication.

CF: cystic fibrosis

Characteristics of ongoing studies *[ordered by study ID]*

NCT01851694

Study name	Determination of Beta-cell Responsiveness to the Incretin Hormones GLP-1 and GIP in Cystic Fibrosis.
Methods	RCT; quadruple blind (participant, care provider, investigator, outcomes assessor); single intervention; 2 centres in USA. Described as parallel design, but test results from same participants are to be compared when receiving active or placebo interventions i.e. cross-over.
Participants	Estimated enrolment: 45 participants. Age: 18 years and above. Gender: both.
Interventions	After the first injection of arginine, a glucose infusion will be started in order to raise the level of sugar in the blood to 230 mg/dl. Once the level is achieved, arginine will be injected again and blood samples are measured. After a 2-hour break, the glucose infusion will be started to achieve a blood sugar of 340mg/dL and arginine injection will be repeated. **Group 1**: 90-minute infusion of the incretin GLP-1 (during the GPA for 230 mg/dL glucose levels); the GPA test will be performed for the 340 mg/dL glucose levels, but no incretin will be infused during this part of the test. **Placebo 1**: 90-minute infusion of saline or salt containing solution. **Group 2**: 90-minute infusion of the incretin GIP (during the GPA for 230 mg/dL glucose levels); the GPA test will be performed for the 340 mg/dL glucose levels but no incretin will be infused during this part of the test. **Placebo 2**: 90-minute infusion of saline or salt containing solution.
Outcomes	**Primary outcome**: 2nd-phase insulin response during GPA test [Time Frame: 5 hours]

NCT01851694 *(Continued)*

	Secondary outcome: change in insulin secretion among CF groups (Ind-GT, IGT, and early CFRD) [Time Frame: 5 hours]
Starting date	Start date: May 2013. Estimated primary completion date: June 2020. Estimated study completion date: December 2020.
Contact information	Prinicipal investigator: Michael R. Rickels, MD, MS, University of Pennsylvania Contacts: Christina Kubrak (kubrak@email.chop.edu) and Kathryn Gallagher (Kathryn.Gallagher2@pennmedicine.upenn.edu).
Notes	Comparison of responses with incretin versus placebo will be performed using statistical methods, specifically, paired t-test or Wilcoxon matched pair test.

NCT02202876

Study name	Redox Imbalance and the Development of Cystic Fibrosis Diabetes (Redoxy).
Methods	RCT; parallel design; single blind (participant); single centre USA.
Participants	Estimated enrolment: 98 participants. Age: over 1 year. Includes healthy age-matched controls.
Interventions	**Group 1**: children with CF aged 1 - 9 years with normal glucose tolerance to receive 1.75 g/kg to a maximum of 75 gm of an oral glucose solution for OGTT. **Group 2**: age-matched control children (1 - 9 years) to receive 1.75 gm/kg to a maximum of 75 g of an oral glucose solution for OGTT. **Group 3**: teenagers (12 years and over) with CF with normal glucose tolerance to eat a high GI meal i.e. isocaloric breakfasts with GI of 80, the nutrient composition of each meal will be 10 kcal/kg, 50% kcal from carbohydrates, 20% kcal from protein, and 30% kcal from fat. **Group 4**: teenagers (12 years and over) with CF with normal glucose tolerance to eat a low GI meal i.e. isocaloric breakfasts with GI of 30, the nutrient composition of each meal will be 10 kcal/kg, 50% kcal from carbohydrates, 20% kcal from protein, and 30% kcal from fat.
Outcomes	**Primary outcome**: acute oxidation (cysteine/cysteine ratio) [Time Frame: Up to 3 hours]
Starting date	Start date: November 2014. Estimated primary completion date: September 2019. Estimated study completion date: September 2019.
Contact information	Principal Investigator: Arlene Stecenko MD (astecen@emory.edu), Children's Healthcare of Atlanta and Emory University, Atlanta, Georgia, USA. Contact: Joy Dangerfield (jdanger@emory.edu).
Notes	Data from healthy controls not eligible for inclusion in the review.

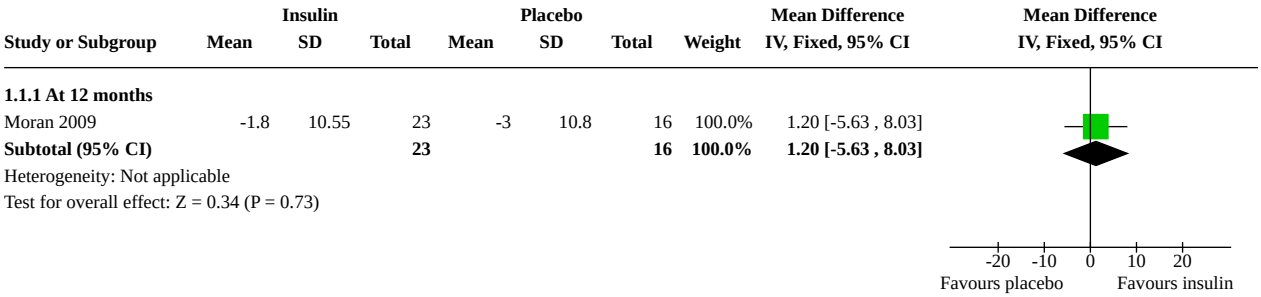
CF: cystic fibrosis
CFRD: cystic fibrosis-related diabetes
GI: glycemic index
GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like-peptide-1
GPA: glucose-potentiated arginine
IGT: impaired glucose tolerance
Ind-GT: indeterminate glucose tolerance
OGTT: oral glucose tolerance test
RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Insulin versus placebo

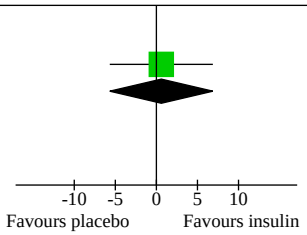
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in FEV_1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 At 12 months	1	39	Mean Difference (IV, Fixed, 95% CI)	1.20 [-5.63, 8.03]
1.2 Change in FVC (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 At 12 months	1	39	Mean Difference (IV, Fixed, 95% CI)	0.60 [-5.67, 6.87]
1.3 Change in BMI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 At 12 months	1	39	Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.23, 1.05]
1.4 Hypoglycemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 At 2 months	1	14	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.23, 17.34]
1.4.2 At 3 months	1	55	Risk Ratio (M-H, Fixed, 95% CI)	9.23 [0.53, 159.14]

Analysis 1.1. Comparison 1: Insulin versus placebo, Outcome 1: Change in FEV_1 (% predicted)



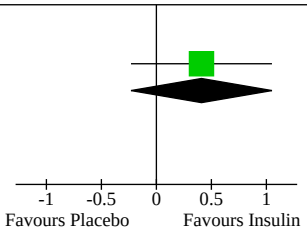
Analysis 1.2. Comparison 1: Insulin versus placebo, Outcome 2: Change in FVC (% predicted)

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 At 12 months								
Moran 2009	-0.5	9.59	23	-1.1	10	16	100.0%	0.60 [-5.67 , 6.87]
Subtotal (95% CI)			**23**			**16**	**100.0%**	**0.60 [-5.67 , 6.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								



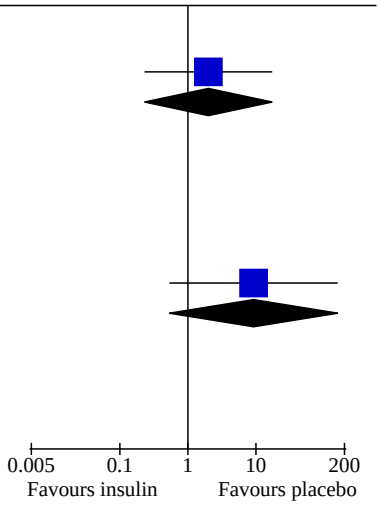
Analysis 1.3. Comparison 1: Insulin versus placebo, Outcome 3: Change in BMI

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 At 12 months								
Moran 2009	0.39	1.01	23	-0.02	1	16	100.0%	0.41 [-0.23 , 1.05]
Subtotal (95% CI)			**23**			**16**	**100.0%**	**0.41 [-0.23 , 1.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								



Analysis 1.4. Comparison 1: Insulin versus placebo, Outcome 4: Hypoglycemia

Study or Subgroup	Insulin Events	Insulin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 At 2 months						
Moran 2001	2	7	1	7	100.0%	2.00 [0.23 , 17.34]
Subtotal (95% CI)		**7**		**7**	**100.0%**	**2.00 [0.23 , 17.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.4.2 At 3 months						
Moran 2009	5	30	0	25	100.0%	9.23 [0.53 , 159.14]
Subtotal (95% CI)		**30**		**25**	**100.0%**	**9.23 [0.53 , 159.14]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						

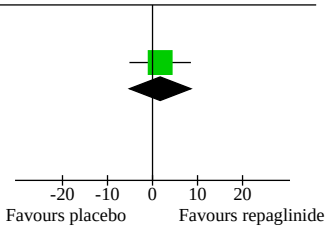


Comparison 2. Repaglinide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in FEV_1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1.1 At 12 months	1	38	Mean Difference (IV, Fixed, 95% CI)	1.70 [-5.13, 8.53]
2.2 Change in FVC (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.2.1 At 12 months	1	38	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-7.40, 5.40]
2.3 Change in BMI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 At 12 months	1	38	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.47, 0.81]
2.4 Hypoglycemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 At 2 months	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.08, 13.02]
2.4.2 At 3 months	1	51	Risk Ratio (M-H, Fixed, 95% CI)	12.52 [0.74, 211.20]

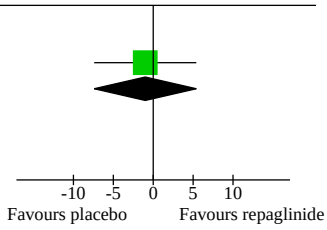
Analysis 2.1. Comparison 2: Repaglinide versus placebo, Outcome 1: Change in FEV_1 (% predicted)

Study or Subgroup	Repaglinide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 At 12 months								
Moran 2009	-1.3	10.32	22	-3	10.8	16	100.0%	1.70 [-5.13 , 8.53]
Subtotal (95% CI)			**22**			**16**	**100.0%**	**1.70 [-5.13 , 8.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								



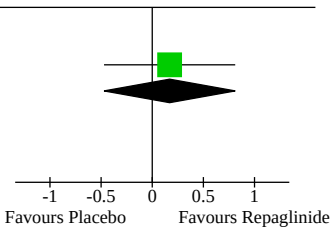
Analysis 2.2. Comparison 2: Repaglinide versus placebo, Outcome 2: Change in FVC (% predicted)

Study or Subgroup	Repaglinide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 At 12 months								
Moran 2009	-2.1	9.85	22	-1.1	10	16	100.0%	-1.00 [-7.40 , 5.40]
Subtotal (95% CI)			**22**			**16**	**100.0%**	**-1.00 [-7.40 , 5.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								



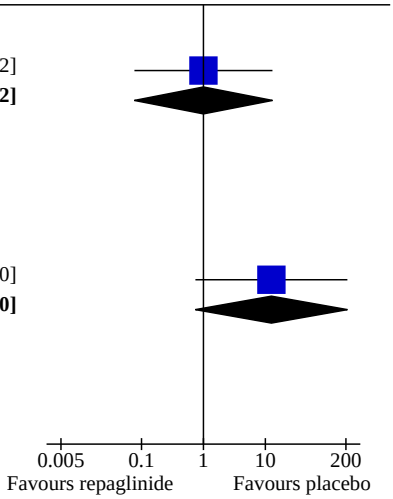
Analysis 2.3. Comparison 2: Repaglinide versus placebo, Outcome 3: Change in BMI

Study or Subgroup	Repaglinide Mean	Repaglinide SD	Repaglinide Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 At 12 months								
Moran 2009	0.15	0.99	22	-0.02	1	16	100.0%	0.17 [-0.47 , 0.81]
Subtotal (95% CI)			**22**			**16**	**100.0%**	**0.17 [-0.47 , 0.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								



Analysis 2.4. Comparison 2: Repaglinide versus placebo, Outcome 4: Hypoglycemia

Study or Subgroup	Repaglinide Events	Repaglinide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 At 2 months						
Moran 2001	1	7	1	7	100.0%	1.00 [0.08 , 13.02]
Subtotal (95% CI)		**7**		**7**	**100.0%**	**1.00 [0.08 , 13.02]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.4.2 At 3 months						
Moran 2009	6	26	0	25	100.0%	12.52 [0.74 , 211.20]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**12.52 [0.74 , 211.20]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.6%						

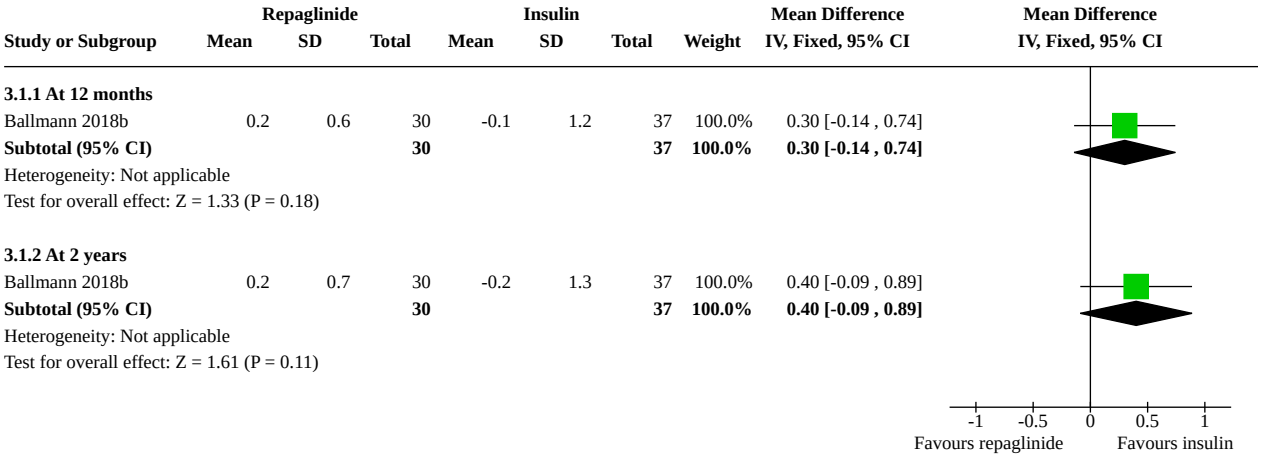


Comparison 3. Insulin versus repaglinide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Change in HbA1c concentration (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1.1 At 12 months	1	67	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.14, 0.74]
3.1.2 At 2 years	1	67	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.09, 0.89]
3.2 Change in FEV_1 (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2.1 At 12 months	2	112	Mean Difference (IV, Fixed, 95% CI)	-0.51 [-4.22, 3.20]
3.2.2 At 2 years	1	67	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-4.12, 3.92]

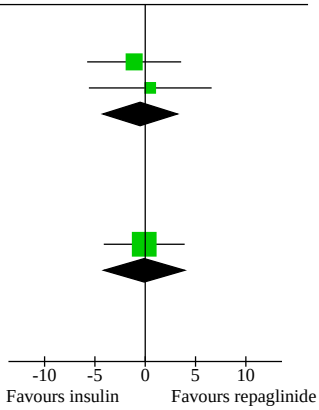
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Change in FVC (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.3.1 At 12 months	2	112	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-4.29, 2.29]
3.3.2 At 2 years	1	67	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-7.37, 0.57]
3.4 Change in BMI	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 Change in BMI z score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5.2 At 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Hypoglycemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.1 At 2 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.2 At 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Insulin versus repaglinide, Outcome 1: Change in HbA1c concentration (%)



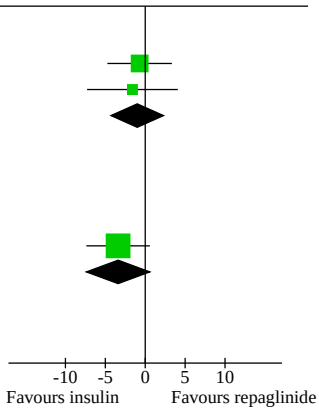
Analysis 3.2. Comparison 3: Insulin versus repaglinide, Outcome 2: Change in FEV_1 (% predicted)

Study or Subgroup	Repaglinide Mean	SD	Total	Insulin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 At 12 months								
Ballmann 2018b	-2.8	8.7	30	-1.7	10.8	37	63.0%	-1.10 [-5.77 , 3.57]
Moran 2009	-1.3	10.32	22	-1.8	10.55	23	37.0%	0.50 [-5.60 , 6.60]
Subtotal (95% CI)			**52**			**60**	**100.0%**	**-0.51 [-4.22 , 3.20]**
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.79)								
3.2.2 At 2 years								
Ballmann 2018b	-3.3	6.2	30	-3.2	10.4	37	100.0%	-0.10 [-4.12 , 3.92]
Subtotal (95% CI)			**30**			**37**	**100.0%**	**-0.10 [-4.12 , 3.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								



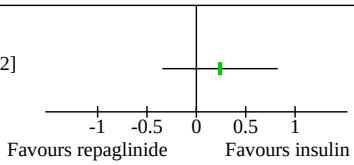
Analysis 3.3. Comparison 3: Insulin versus repaglinide, Outcome 3: Change in FVC (% predicted)

Study or Subgroup	Repaglinide Mean	SD	Total	Insulin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 At 12 months								
Ballmann 2018b	-1.5	6.3	30	-0.8	10.4	37	66.4%	-0.70 [-4.74 , 3.34]
Moran 2009	-2.1	9.85	22	-0.5	9.59	23	33.6%	-1.60 [-7.28 , 4.08]
Subtotal (95% CI)			**52**			**60**	**100.0%**	**-1.00 [-4.29 , 2.29]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.60 (P = 0.55)								
3.3.2 At 2 years								
Ballmann 2018b	-4	7.4	30	-0.6	9.2	37	100.0%	-3.40 [-7.37 , 0.57]
Subtotal (95% CI)			**30**			**37**	**100.0%**	**-3.40 [-7.37 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								



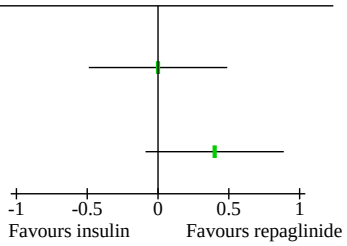
Analysis 3.4. Comparison 3: Insulin versus repaglinide, Outcome 4: Change in BMI

Study or Subgroup	Repaglinide Mean	SD	Total	Insulin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.4.1 At 12 months							
Moran 2009	0.39	1.01	23	0.15	0.99	22	0.24 [-0.34 , 0.82]



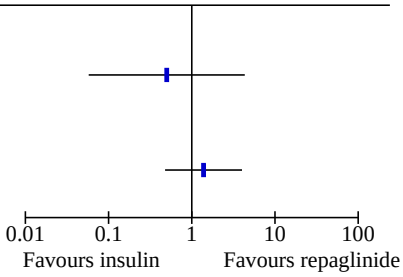
Analysis 3.5. Comparison 3: Insulin versus repaglinide, Outcome 5: Change in BMI z score

Study or Subgroup	Repaglinide Mean	SD	Total	Insulin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.5.1 At 12 months							
Ballmann 2018b	-0.7	1.1	30	-0.7	0.9	37	0.00 [-0.49 , 0.49]
3.5.2 At 2 years							
Ballmann 2018b	0.2	0.7	30	-0.2	1.3	37	0.40 [-0.09 , 0.89]



Analysis 3.6. Comparison 3: Insulin versus repaglinide, Outcome 6: Hypoglycemia

Study or Subgroup	Repaglinide Events	Total	Insulin Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.6.1 At 2 months					
Moran 2001	1	7	2	7	0.50 [0.06 , 4.33]
3.6.2 At 3 months					
Moran 2009	6	26	5	30	1.38 [0.48 , 4.01]



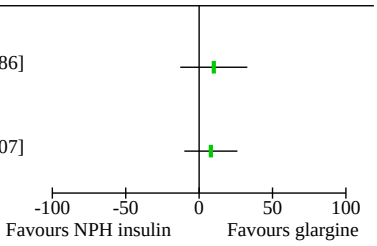
Comparison 4. NPH insulin versus glargine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Glucose levels (mg/dl)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1.1 Fasting (at 3 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1.2 2 hour post-prandial (at 3 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2 Change in weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3 Fat mass by DEXA (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4 Lean mass by DEXA (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5 Hypoglycemic events per participant	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

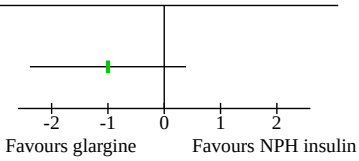
Analysis 4.1. Comparison 4: NPH insulin versus glargine, Outcome 1: Glucose levels (mg/dl)

Study or Subgroup	NPH insulin Mean	SD	Total	Glargine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.1.1 Fasting (at 3 months)								
Grover 2008	50	43.6	19	40	26.16	19	10.00 [-12.86 , 32.86]	
4.1.2 2 hour post-prandial (at 3 months)								
Grover 2008	91	30.52	19	83	26.16	19	8.00 [-10.07 , 26.07]	



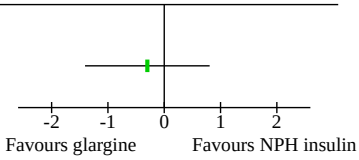
Analysis 4.2. Comparison 4: NPH insulin versus glargine, Outcome 2: Change in weight (kg)

Study or Subgroup	NPH insulin Mean	SD	Total	Glargine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.2.1 At 3 months								
Grover 2008	0.2	2.18	19	1.2	2.18	19	-1.00 [-2.39 , 0.39]	



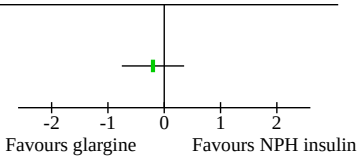
Analysis 4.3. Comparison 4: NPH insulin versus glargine, Outcome 3: Fat mass by DEXA (kg)

Study or Subgroup	NPH insulin Mean	SD	Total	Glargine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.3.1 At 3 months								
Grover 2008	0.4	1.74	19	0.7	1.74	19	-0.30 [-1.41 , 0.81]	



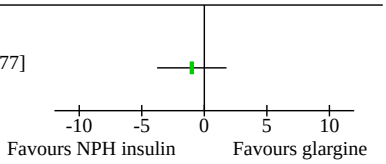
Analysis 4.4. Comparison 4: NPH insulin versus glargine, Outcome 4: Lean mass by DEXA (kg)

Study or Subgroup	NPH insulin Mean	SD	Total	Glargine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.4.1 At 3 months								
Grover 2008	0.1	0.87	19	0.3	0.87	19	-0.20 [-0.75 , 0.35]	



Analysis 4.5. Comparison 4: NPH insulin versus glargine, Outcome 5: Hypoglycemic events per participant

Study or Subgroup	NPH insulin Mean	NPH insulin SD	NPH insulin Total	Glargine Mean	Glargine SD	Glargine Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.5.1 At 3 months								
Grover 2008	5	4.36	19	6	4.36	19	-1.00 [-3.77 , 1.77]	



APPENDICES

Appendix 1. Additional search strategies

Database	Search terms	Date searched
PubMed (www.ncbi.nlm.nih.gov/pubmed)	#1 randomized controlled trial [pt] #2 controlled clinical trial [pt] #3 randomized [tiab] #4 placebo [tiab] #5 drug therapy [sh] #6 randomly [tiab] #7 trial [tiab] #8 groups [tiab] #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 #10 animals [mh] NOT humans [mh] #11 #9 NOT #10 #12 cystic fibrosis [MeSH Terms] OR "cystic fibrosis" [af] OR mucoviscidosis [af] OR mucoviscidose [af] #13 diabetes OR diabetic [af] #14 #11 AND #12 AND #13 **NOTE: Lines #1- #11 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format*	21 March 2020
ClinicalTrials.gov (ClinicalTrials.gov)	**[Advanced Search]** CONDITION/ DISEASE: cystic fibrosis OTHER TERMS: diabetes STUDY TYPE: Interventional Studies	21 March 2020

(Continued)

WHO ICTRP (apps.who.int/trialsearch)	**[Basic Search]** cystic fibrosis AND diabetes *[WHO ICTRP REGISTER NOT WORKING AT THE MOMENT. SEARCH TERMS NEED TO BE TESTED ONCE THE REGISTER IS UP AND RUNNING]*	Search attempted 17 May 2020, database unavailable due to Covid

WHAT'S NEW

Date	Event	Description
10 September 2020	New citation required but conclusions have not changed	The title of this review has been changed to reflect the inclusion of all drug treatments for managing cystic fibrosis-related diabetes. Despite the identification of new references, no data have been added to the review and our conclusions remain the same.
10 September 2020	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register and additional online searching identified 12 new references which were potentially eligible for inclusion in the review. One reference was an additional reference (full paper) to an already included study (Ballmann 2018b). Six were references to newly excluded studies (Eiel 2018; Geyer 2019; NCT01149005; NCT02496780; Sc 2010) and three were additional references to two already excluded studies (Beaudoin 2015; Minicucci 2012). Two trials each with a single reference are currently listed as ongoing (NCT01851694; NCT02202876). Summary of findings tables have been added for each comparison presented in this review.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 3, 2005

Date	Event	Description
4 April 2016	New citation required but conclusions have not changed	Despite the inclusion of a new trial in this version of the review, there were limited trial data available and these have not changed the conclusions of the review.
4 April 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified six references to three potentially eligible trials. One trial has been included in the review (Ballmann 2018b), the second is currently listed as 'Awaiting classification' until more details are published (de Lind 2014) and the third has been excluded (Beaudoin 2015). The format of the Plain Language Summary has been updated in line with current Cochrane guidance.

Date	Event	Description
22 July 2013	New citation required and conclusions have changed	While we are still not able to provide recommendations for treatment based on evidence from randomised controlled trials, we have increased the information available within this review (including a new treatment comparison) and revised our recommendations for future research.
22 July 2013	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified seven references to four separate studies which were potentially eligible for inclusion in this review; two of these studies (one reference each) have been included (Grover 2008; Moran 2009), while a randomized control trial of a long-acting insulin, was excluded as it only studied cystic fibrosis patients with glucose intolerance and not patients with CFRD (Minicucci 2012); a further study was excluded as it was a study of methods to improve adherence to therapy in children with Type 1 diabetes or cystic fibrosis rather than a comparison of different treatments for cystic fibrosis-related diabetes (Driscoll 2009). Additional searching identified a further study which has been excluded (Hardin 2009).
4 February 2009	Amended	Contact details updated
1 April 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references eligible for inclusion in this review. A review which was previously excluded has been re-examined and is now included in this update (Moran 2001).
1 April 2008	Amended	Converted to new review format.
21 May 2007	New search has been performed	The new search identified eight new references to four studies (Borowitz 2005; Konig 2005; Onady 2006; Sulli 2006). None of which was eligible for inclusion in the review and are all listed under 'Excluded studies'.
10 April 2006	New search has been performed	The new search identified six new references. However, none of these were eligible for inclusion in the review.
25 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Gary Onady conceived the review and drafted the protocol and the full review with additional comments from Adrienne Stolfi.

Gary Onady is responsible for the updates of the review and acts as guarantor of the review.

DECLARATIONS OF INTEREST

Gary Onady served on the Cystic Fibrosis Related Diabetes Guideline committee, with these Guidelines published in Diabetes Care in December 2010. He wrote the management component of that manuscript. This position has in no way influenced this subsequent and more recent review. In fact, this review puts into question the recommendations made in that earlier publication. He also serves on the Cystic Fibrosis Foundation's Center Committee, whose work is totally devoted to the clinical accreditation of CF Centers across the USA, and does not involve details as to the subject matter involved in this Cochrane Review. He has received travel and accomodation expenses from the Cystic Fibrosis Foundation.

Adrienne Stolfi declares no known potential conflict of interest.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Original review

In a post hoc change the comparator group 'oral anti-diabetic agents' were separately listed as follows:

1. sulphonyureas and related agents
2. biguanides and related agents
3. glitazones and related agents
4. other agents that specifically manage hyperglycemia.

We originally thought that studies comparing active treatment to placebo would not be undertaken on ethical grounds, however, this proved not to be the case and we have amended our inclusion criteria accordingly.

2013 update

1. The outcome 'Clinical status' has been added as *post hoc* change at the 2013 update as the authors feel that the six-minute walk test is a more significant measure when powering of studies include low patient numbers. The outcome HRQoL has also been included under 'Clinical status'. Mortality was moved from primary to secondary outcomes as a result of editorial changes regarding the numbers of primary outcome measures allowed.

2. The secondary outcome "Prevalence of secondary infection complications (*Pseudomonas aeruginosa/Burkholderia cepacia/ Staphylococcus aureus*)" has been replaced with the outcome "Rate of pulmonary exacerbations".

2019 update

In a post hoc change we also included injectable medications as an intervention.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Bias; Blood Glucose [analysis]; Carbamates [administration & dosage]; Cystic Fibrosis [blood] [*complications]; Diabetes Mellitus [blood] [*drug therapy] [etiology]; Fasting [blood]; Hyperglycemia [drug therapy]; Hypoglycemic Agents [*administration & dosage]; Insulin [*administration & dosage]; Insulin Glargine [administration & dosage]; Insulin, Isophane [administration & dosage]; Piperidines [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans