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Alpha-glucosidase inhibitors for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus (Review)

Moelands SVL, Lucassen PLBJ, Akkermans RP, De Grauw WJC, Van de Laar FA

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[Intervention Review]

Alpha-glucosidase inhibitors for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus

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ABSTRACT

Background

Alpha-glucosidase inhibitors (AGI) reduce blood glucose levels and may thus prevent or delay type 2 diabetes mellitus (T2DM) and its associated complications in people at risk of developing of T2DM.

Objectives

To assess the effects of AGI in people with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), moderately elevated glycosylated haemoglobin A1c (HbA1c) or any combination of these.

Search methods

We searched CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the reference lists of systematic reviews, articles and health technology assessment reports. The date of the last search of all databases was December 2017.

Selection criteria

We included randomised controlled trials (RCTs), with a duration of one year or more, comparing AGI with any pharmacological glucose-lowering intervention, behaviour-changing intervention, placebo or no intervention in people with IFG, IGT, moderately elevated HbA1c or combinations of these.

Data collection and analysis

Two review authors read all abstracts and full-text articles or records, assessed quality and extracted outcome data independently. One review author extracted data, which were checked by a second review author. We resolved discrepancies by consensus or involvement of a third review author. For meta-analyses we used a random-effects model with assessment of risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, using 95% confidence intervals (CIs) for effect estimates. We assessed the overall quality of the evidence by using the GRADE instrument.

Main results

For this update of the Cochrane Review (first published 2006, Issue 4) we included 10 RCTs (11,814 participants), eight investigating acarbose and two investigating voglibose, that included people with IGT or people "at increased risk for diabetes". The trial duration ranged from one to six years. Most trials compared AGI with placebo (N = 4) or no intervention (N = 4).

Acarbose reduced the incidence of T2DM compared to placebo: 670 out of 4014 people (16.7%) in the acarbose groups developed T2DM, compared to 812 out of 3994 people (20.3%) in the placebo groups (RR 0.82, 95% CI 0.75 to 0.89; $P < 0.0001$; 3 trials; 8008 participants; moderate-certainty evidence). One trial including participants with coronary heart disease and IGT contributed 64% of cases for this outcome. Acarbose reduced the risk of T2DM compared to no intervention: 7 out of 75 people (9.3%) in the acarbose groups developed T2DM, compared to 18 out of 65 people (27.7%) in the no-intervention groups (RR 0.31, 95% CI 0.14 to 0.69; $P = 0.004$; 2 trials; 140 participants; very low-certainty evidence).

Acarbose compared to placebo did not reduce or increase the risk of all-cause mortality (RR 0.98, 95% CI 0.82 to 1.18; $P = 0.86$; 3 trials; 8069 participants; very low-certainty evidence), cardiovascular mortality (RR 0.88; 95% CI 0.71 to 1.10; $P = 0.26$; 3 trials; 8069 participants; very low-certainty evidence), serious adverse events (RR 1.12, 95% CI 0.97 to 1.29; $P = 0.13$; 2 trials; 6625 participants; low-certainty evidence), non-fatal stroke (RR 0.50, 95% CI 0.09 to 2.74; $P = 0.43$; 1 trial; 1368 participants; very low-certainty evidence) or congestive heart failure (RR of 0.87; 95% CI 0.63 to 1.12; $P = 0.40$; 2 trials; 7890 participants; low-certainty evidence). Acarbose compared to placebo reduced non-fatal myocardial infarction: one out of 742 participants (0.1%) in the acarbose groups had a non-fatal myocardial infarction compared to 15 out of 744 participants (2%) in the placebo groups (RR 0.10, 95% CI 0.02 to 0.53; $P = 0.007$; 2 trials; 1486 participants; very low-certainty evidence). Acarbose treatment showed an increased risk of non-serious adverse events (mainly gastro-intestinal events), compared to placebo: 751 of 775 people (96.9%) in the acarbose groups experienced an event, compared to 723 of 775 people (93.3%) in the placebo groups (RR 1.04; 95% CI 1.01 to 1.06; $P = 0.0008$; 2 trials; 1550 participants). Acarbose compared to no intervention showed no advantage or disadvantage for any of these outcome measures (very low-certainty evidence).

One trial each compared voglibose with placebo (1780 participants) or diet and exercise (870 participants). Voglibose compared to placebo reduced the incidence of T2DM: 50 out of 897 participants (5.6%) developed T2DM, compared to 106 out of 881 participants (12%) in the placebo group (RR 0.46, 95% CI 0.34 to 0.64; $P < 0.0001$; 1 trial; 1778 participants; low-certainty evidence). For all other reported outcome measures there were no clear differences between voglibose and comparator groups. One trial with 90 participants compared acarbose with diet and exercise and another trial with 98 participants reported data on acarbose versus metformin. There were no clear differences for any outcome measure between these two acarbose interventions and the associated comparator groups.

None of the trials reported amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, health-related quality of life, time to progression to T2DM, or socioeconomic effects.

Authors' conclusions

AGI may prevent or delay the development of T2DM in people with IGT. There is no firm evidence that AGI have a beneficial effect on cardiovascular mortality or cardiovascular events.

PLAIN LANGUAGE SUMMARY

Alpha-glucosidase inhibitors for prevention or delay of type 2 diabetes and associated complications in people at increased risk of type 2 diabetes

Review question

Can alpha-glucosidase inhibitors prevent or delay type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus?

Background

People with moderately elevated glucose levels are often said to be at an increased risk of developing type 2 diabetes. Therefore, these people are frequently recommended to increase exercise and lower calorie intake to prevent type 2 diabetes. Alpha-glucosidase inhibitors (acarbose, miglitol, voglibose), are used to lower blood glucose in people with type 2 diabetes mellitus. It is currently not known whether alpha-glucosidase inhibitors should be prescribed for people with moderately raised blood glucose levels. We wanted to find out whether alpha-glucosidase inhibitors could prevent or delay type 2 diabetes mellitus in people with moderately elevated glucose levels. We searched medical literature for randomised controlled trials (clinical trials where people are randomly put into one of two or more treatment groups), of at least one year's duration, investigating alpha-glucosidase inhibitors in participants with glucose levels higher than considered normal, but below the diagnostic criteria for type 2 diabetes mellitus.

Trial characteristics

We found 10 randomised controlled trials representing 11,814 participants, eight investigating acarbose and two investigating voglibose. The trial duration ranged from one to six years.

This evidence is up to date as of December 2017.

Key results

When comparing acarbose with placebo (a substance thought to have no therapeutic effect), 670 out of 4014 participants (17%) receiving acarbose developed type 2 diabetes, compared to 812 out of 3994 participants (20%) receiving placebo. Most data for this comparison came from a trial including people with heart disease. When comparing acarbose with no intervention, seven out of 75 participants (9%) receiving acarbose developed type 2 diabetes, compared to 18 out of 65 participants (28%) receiving no intervention. Acarbose treatment did not reduce or increase the risk of death from any cause, death from heart disease, serious side effects, strokes or heart failure. Compared to placebo, acarbose reduced the risk for heart attacks (one out of 742 participants (0.1%) receiving acarbose had a heart attack compared to 15 out of 744 participants (2%) receiving placebo). Acarbose treatment showed an increased risk of non-serious side effects (mainly gastro-intestinal events), compared to placebo: 751 of 775 people (97%) receiving acarbose had a non-serious side effect, compared to 723 of 775 people (93%) receiving placebo.

One trial compared voglibose with placebo and another trial compared voglibose with diet and exercise. When comparing voglibose with placebo, 50 out of 897 participants (5.6%) receiving voglibose developed type 2 diabetes, compared to 106 out of 881 participants (12%) receiving placebo.

One trial with 90 participants compared acarbose with diet and exercise and another trial with 98 participants compared acarbose with metformin. There were no important differences for any outcome for these comparisons.

None of the trials reported amputation of lower limbs, blindness or severe vision loss, kidney disease, health-related quality of life, time to progression to type 2 diabetes mellitus, or socioeconomic effects (such as absence from work or costs).

Quality of the evidence

For most of our outcomes we are uncertain or very uncertain how valid the results of our comparisons are. Reasons for this uncertainty are systematic errors in some of the included trials, the overall low number of trials for a particular outcome, imprecise results and missing data of one included trial.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Acarbose compared to placebo

Acarbose for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk of developing of type 2 diabetes mellitus

Population: people at risk of developing type 2 diabetes mellitus

Settings: outpatients

Intervention: alpha-glucosidase inhibitors (acarbose)

Comparison: placebo

Outcomes	Placebo	Acarbose	Relative effect (95% CI)	Number of participants Trials	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 3-5 years	56 per 1000	55 per 1000 (44 to 66)	RR 0.98 (0.82 to 1.18)	8069 3 RCTs	⊕⊕⊕⊕ Very low^a	-
Incidence of T2DM Follow-up: 3-5 years Definition of intermediate hyperglycaemia (definition of T2DM incidence): ACE 2017 : FPG < 7.0 mmol/L; 2hPG ≥ 7.8 - < 11.1 mmol/L (FPG ≥ 7.0 mmol/L; 2hPG ≥ 11.1 mmol/L) DAISI 2008 : FPG < 7.8 mmol/L; 2hPG 7.8–11.1 mmol/L; HbA1c ≤ 7.0% (FPG ≥ 7.8 mmol/L; 2hPG ≥ 11.1 mmol/L) STOP-NIDDM 2002 : FPG 5.6-7.7 mmol/L; 2hPG ≥ 7.8 ≤ 11.1 mmol/L (2hPG ≥ 11.1 mmol/L)	203 per 1000	167 per 1000 (152 to 181)	RR 0.82 (0.75 to 0.89) (95% prediction interval: 0.48 to 1.40)	8008 3 RCTs	⊕⊕⊕⊕ Moderate^b	ACE 2017 included participants with coronary heart disease and contributed 64.0% of cases
Serious adverse events Follow-up: 3.3-5 years	95 per 1000	106 per 1000 (92 to 122)	RR 1.12 (0.97 to 1.29)	6625 2 RCTs	⊕⊕⊕⊕ Low^c	-
Cardiovascular mortality Follow-up: 3.3-5 years	42 per 1000	37 per 1000 (29 to 46)	RR 0.88 (0.71 to 1.10)	8069 3 RCTs	⊕⊕⊕⊕ Very low^a	-

(a) Non-fatal myocardial infarction	(a) 20 per 1000	(a) 1 per 1000 (0 to 11)	(a) RR 0.10 (0.02 to 0.53)	(a) 1486	(a) ⊕⊕⊕⊕	-
(b) Non-fatal stroke	(b) 6 per 1000			2 RCTs	Very low^d	
(c) Congestive heart failure	(c) 19 per 1000	(b) 3 per 1000 (1 to 16)	(b) RR 0.50 (0.09 to 2.74)	(b) 1368	(b) ⊕⊕⊕⊕	Very low^d
Follow-up: 3.3 years		(c) 16 per 1000 (12 to 21)	(c) RR 0.87 (0.63 to 1.12)	1 RCT (c) 7890 2 RCTs	(c) ⊕⊕⊕⊕	Low^e
Health-related quality of life	Not reported					
Socioeconomic effects	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

2hPG: 2-hour plasma glucose; **CI:** confidence interval; **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **IGT:** impaired glucose tolerance; **RCT:** randomised controlled trial; **RR:** risk ratio; **T2DM:** type 2 diabetes mellitus

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level because of inconsistency in direction of effect and by two levels because of serious imprecision (confidence interval consistent with benefit and harm and small number of trials). See [Appendix 17](#).

^bDowngraded by one level because of imprecision (small number of trials). See [Appendix 17](#).

^cDowngraded by two levels because of serious imprecision (confidence interval consistent with benefit and harm and small number of trials). See [Appendix 17](#).

^dDowngraded by two levels because of serious risk of bias (attrition bias and reporting bias), and by one level because of imprecision (small number of trials). See [Appendix 17](#).

^eDowngraded by two levels because of serious imprecision (confidence interval consistent with benefit and harm and small number of trials). See [Appendix 17](#).

Summary of findings 2. Acarbose compared to no intervention

Acarbose for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk of developing type 2 diabetes mellitus

Population: people at risk of developing type 2 diabetes mellitus

Settings: outpatients

Intervention: alpha-glucosidase inhibitors (acarbose)

Comparison: no intervention

Outcomes	No interven- tion	Acarbose	Relative effect (95% CI)	Number of par- ticipants Trials	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1-5 years	See comment			171 2 RCTs	⊕⊕⊕⊕ Very low^a	2 of 4 trials re- ported mortal- ity. No deaths occurred.
Incidence of T2DM Follow-up: 1-5 years Definition of intermediate hyperglycaemia (definition of T2DM incidence): Fang 2004 and Wang 2000 : FPG < 7.8 mmol/L; 2hPG ≥ 7.8 ≤ 11.1 mmol/L (FPG ≥ 7.8 mmol/L; 2hPG ≥ 11.1 mmol/L)	277 per 1000	86 per 1000 (39 to 191)	RR 0.31 (0.14 to 0.69)	140 2 RCTs	⊕⊕⊕⊕ Very low^b	-
Serious adverse events	Not reported					
Cardiovascular mortality Follow-up: 1-4.5 years	49 per 1000	31 per 1000 (8 to 124)	RR 0.64 (0.16 to 2.56)	205 2 RCTs	⊕⊕⊕⊕ Very low^c	-
(a) Non-fatal myocardial infarction (b) Non-fatal stroke (c) Congestive heart failure Follow-up: 1-4.5 years	(a) 68 per 1000 (b) 39 per 1000 (c) 58 per 1000	(a) 20 per 1000 (5 to 96) (b) 21 per 1000 (4 to 109) (c) 51 per 1000 (16 to 159)	(a) RR 0.30 (0.07 to 1.41) (b) RR 0.53 (0.10 to 2.81) (c) RR 0.87 (0.27 to 2.73)	(a) 205 2 RCTs (b) 205 2 RCTs (c) 205 2 RCTs	(a) ⊕⊕⊕⊕ Very low^c (b) ⊕⊕⊕⊕ Very low^c (c) ⊕⊕⊕⊕ Very low^c	-
Health-related quality of life	Not reported					
Socioeconomic effects	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

2hPG: 2-hour plasma glucose; **CI:** confidence interval; **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **RCT:** randomised controlled trials; **RR:** risk ratio; **T2DM:** type 2 diabetes mellitus

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level because of risk of bias (unclear selection bias and selective reporting), and by two levels because of serious imprecision (small number of trials, small sample size and the outcome not being a common event). See [Appendix 18](#).

^bDowngraded by one level because of risk of bias (unclear selection bias and selective reporting), and by two levels because of serious imprecision (small number of trials and small sample size). See [Appendix 18](#).

^cDowngraded by one level because of risk of bias (unclear selection bias and selective reporting), and by two levels because of serious imprecision (small number of trials, small sample size and CI consistent with benefit and harm). See [Appendix 18](#).

BACKGROUND

Description of the condition

'Prediabetes' or 'intermediate hyperglycaemia' are terms that are used to indicate a blood glucose level below the cut-off value for diabetes, but higher than is considered normal. It is considered to be a risk factor for the development of type 2 diabetes mellitus (T2DM), with a higher predictive value than other known risk factors, such as obesity or a family history of T2DM (Colditz 1995; Meigs 2000; Nguyen 2011; InterAct Consortium 2013; Tabak 2012).

Intermediate hyperglycaemia is often characterised by various measurements of elevated blood glucose concentrations, such as isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), isolated elevated glycosylated haemoglobin A1c (HbA1c), or combinations thereof (WHO/IDF 2006). IGT is defined by the World Health Organisation (WHO), and the American Diabetes Association (ADA), as plasma glucose concentrations between 7.8 to 11.1 mmol/L (140 to 200 mg/dL), two hours after ingestion of 75 g of glucose. Trials indicate that IGT is caused by insulin resistance and defective insulin secretion (Abdul-Ghani 2006; Jensen 2002). The WHO defines IFG as fasting plasma glucose concentrations between 6.1 to 6.9 mmol/L (110 to 125 mg/dL). The ADA definition has a lower threshold for defining IFG, namely 5.6 mmol/L (100 mg/dL; ADA 2003). IFG seems to be associated with β -cell dysfunction (impaired insulin secretion), and an increase in the hepatic glucose output (DeFronzo 1989). More recently, HbA1c has been introduced to identify people at high risk of developing T2DM. People with HbA1c measurements between 6.0% and 6.4% (42 and 46 mmol/mol) fulfilled this criterion (IEC 2009). Shortly afterwards, the ADA re-defined this HbA1c range as 5.7% to 6.4% (39 and 46 mmol/mol; ADA 2010), a decision not endorsed by the WHO, the International Expert Committee (IEC) or other organisations.

Trials have shown poor correlations between HbA1c and IFG/IGT (Gosmanov 2014; Selvin 2011). Notably, the various glycaemic tests do not seem to identify the same people, as there is an imperfect overlap among the glycaemic modalities available to define intermediate hyperglycaemia (Gosmanov 2014; Selvin 2011). The risk of progression from people at risk of T2DM depends on the diagnostic criteria used to identify the risk. Some people with intermediate hyperglycaemia will never develop T2DM and some people will return to normoglycaemia. IGT is often accepted as the best glycaemic variable to predict progression to T2DM. Trials indicate that fewer than half of the people defined as 'prediabetic' by means of IGT or IFG will develop T2DM in the following 10 years (Morris 2013). Of the people with both IGT and IFG, around 70% is estimated to develop T2DM (Morris 2013). Most importantly, intermediate hyperglycaemia is commonly an asymptomatic condition and consequently often remains 'undiagnosed' (CDC 2015).

In 2017, the International Diabetes Federation (IDF) estimated the prevalence of IGT to be 352 million people and this is predicted to increase to more than half a billion people by 2045. The current prevalence of T2DM is estimated to be 425 million people (IDF 2017). Thus, there is a need to address this growing number of (potential) patients. However, it has not been clarified whether or not any particular intervention, especially glucose-lowering drugs, should be recommended for people with IGT (Yudkin 2014). Trials have indicated that the progression to T2DM is reduced, or possibly only delayed, with behavioural interventions, such as increased physical

activity, dietary changes or both (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009; Finnish Diabetes Prevention Study Group 2001). However, the effect on longer-term development of diabetes is not clear (Dunkley 2014).

Current clinical practice recommends a healthy lifestyle such as regular physical activity, not smoking, and balanced food choices, to prevent the development of T2DM (ADA 2014). International diabetes associations and clinicians do not generally accept the prescription of pharmacological glucose-lowering interventions for the prevention of T2DM. Several groups of pharmacological glucose-lowering interventions have been investigated for people at risk of T2DM. Some findings indicate that the progression to T2DM is reduced or may only be delayed when using these pharmacological interventions (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009). However, the ADA recommends metformin for people at risk of T2DM, especially for those with body mass index over 35 kg/m², aged less than 60 years, and women with prior gestational diabetes mellitus (ADA 2015).

Description of the intervention

Alpha-glucosidase inhibitors (AGI) are reversible inhibitors of alpha-glucosidase, an enzyme present in the brush border of the small intestine. Currently, three AGI exist: acarbose, miglitol and voglibose. AGI delay absorption of complex carbohydrates and thus inhibit postprandial glucose peaks and consequently lower postprandial insulin levels. In the treatment of T2DM AGI have been proven to lower blood glucose and post-load insulin levels but there is no evidence for a reduction of mortality or morbidity (Van de Laar 2005).

Potential adverse effects are of special importance in the use of medications in people with intermediate hyperglycaemia, who are asymptomatic, and would not therefore, in contrast to potential adverse effects, notice any direct benefits from the medication. In addition, because of the chronic and long-lasting character of intermediate hyperglycaemia, medication will have to be used for a long period of time. Therefore, long-term safety is very important.

Adverse effects of the intervention

AGI cause unfavourable dose-dependent adverse effects, mostly flatulence and other gastro-intestinal adverse effects. There is no evidence for long-term detrimental effects of AGI (Caballero 2016; Van de Laar 2005).

How the intervention might work

In people with insulin resistance, post-prandial blood glucose is not properly stored in the muscle, adipose, and liver cells, and hepatic glucose production is not inhibited (Stumvoll 2005). This leads to a post-prandial glucose spike. In the long term, hyperglycaemia increases the risk of microvascular and cardiovascular morbidity (Laakso 1999). AGI prevent hyperglycaemia and thus hyperinsulinaemia, and therefore might decrease the risk of microvascular and cardiovascular morbidities (Turnbull 2009).

The mechanism by which the intervention might prevent T2DM is less clear. As mentioned, AGI lower blood glucose. Consequently, if a person has lower blood glucose due to the medication and therefore does not have T2DM diagnosed, that does not necessarily mean that the underlying cause of T2DM has been treated.

Trials on whether AGI improve insulin sensitivity are contradictory. Multiple trials that compared an AGI to a placebo in people with (early) T2DM found little to no improvement of insulin sensitivity (Jenney 1993; Johnson 1996; Kirkman 2006; Matsumoto 1998). However, other trials found that AGI improved insulin sensitivity (Chiasson 1996; Meneilly 2000; Shinozaki 1996).

Why it is important to do this review

A recent systematic review with network meta-analysis looked at various interventions (behaviour changing, pharmacological and surgical), and their effects in reducing progression to T2DM in people with intermediate hyperglycaemia (Stevens 2015). The most effective interventions according to this review were glipizide (hazard ratio (HR) 0.16, 95% credible interval 0.02 to 1.62), and diet plus pioglitazone (HR 0.17, 95% credible interval 0.09 to 0.33). They also included three trials with AGI as an intervention (Kawamori 2009; Pan 2003; STOP-NIDDM 2002). Their meta-analysis led to a HR of 0.74 (95% confidence interval (CI) 0.57 to 0.93), for acarbose compared to placebo and a HR of 0.39 (95% CI 0.26 to 0.57), for voglibose compared to placebo, suggesting that AGI reduced or delayed the development of T2DM. A more recent Cochrane review looked at the effect of diet, physical activity, or both on delaying or preventing T2DM and its complications. They found that the combination of diet and physical activity reduced the incidence of T2DM in people with IGT compared to standard or no intervention (RR 0.57, 95% CI 0.50 to 0.64) (Hemmingsen 2017a). Other Cochrane Reviews did not find firm evidence that DPP-4 inhibitors, GLP-1 analogues, insulin secretagogues, or SGLT 2 inhibitors delayed or prevented T2DM in people at risk of T2DM (Hemmingsen 2016a; Hemmingsen 2016b; Hemmingsen 2017b).

However, besides the original version of this review (New Reference), there has been no systematic review looking solely at whether AGI are effective (in the long-term), in preventing not only T2DM, but also cardiovascular morbidity and mortality. One review looked at the effect of both pharmacological and behaviour-changing interventions on the prevention of cardiovascular events in people with intermediate hyperglycaemia, and one of the included trials used acarbose as the intervention (STOP-NIDDM 2002). This review concluded that both pharmacological and behaviour-changing interventions prevented or delayed T2DM, but neither prevented nor delayed all-cause and cardiovascular mortality or myocardial infarctions (Hopper 2011).

Intermediate hyperglycaemia is a risk factor for T2DM and is asymptomatic. However, AGI are accompanied by adverse effects. Therefore, treating intermediate hyperglycaemia with AGI can only be justified by strong proof that this treatment does in fact prevent or delay T2DM or its subsequent cardiovascular morbidity and mortality.

OBJECTIVES

To assess the effects of AGI in people with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), moderately elevated glycosylated haemoglobin A1c (HbA1c) or any combination of these.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials with a minimum duration of one year. Because the common adverse effects of AGI make true blinding difficult, we included both blinded and non-blinded trials. We investigated trials published in any language, and all identified trials, published or unpublished.

Types of participants

We included non-diabetic individuals with increased risk of T2DM. We defined increased risk as having the condition of intermediate hyperglycaemia.

Diagnostic criteria for people at risk of T2DM development

To be consistent with changes to the classification of, and diagnostic criteria for intermediate hyperglycaemia (IFG, IGT, and elevated HbA1c), over the years, the diagnosis should have been established using the standard criteria valid at the trial start (e.g. ADA 2010; WHO 1985). Ideally, the diagnostic criteria should have been described. If necessary, we used the trial authors' definition of risk but we contacted trial authors for additional information. Differences in the glycaemic measurements used to define risk may introduce substantial heterogeneity. Therefore we planned to subject the diagnostic criteria to a subgroup analysis.

Types of interventions

We investigated the following comparisons of AGI versus all other pharmacological glucose-lowering interventions, behaviour-changing interventions, placebo or no intervention (usual care).

- AGI as monotherapy compared with any pharmacological glucose-lowering intervention (e.g. metformin, sulphonylurea), behaviour-changing interventions (e.g. diet, exercise, diet and exercise), placebo or no intervention
- AGI as a part of a combination therapy compared with any pharmacological glucose-lowering agent if this glucose-lowering agent was the same in both the intervention and comparator groups (e.g. acarbose + metformin versus metformin)

Other concomitant interventions (e.g. educational programmes or additional pharmacotherapy), had to be the same in both the intervention and comparator groups to establish fair comparisons.

Minimum duration of intervention

We included trials with a duration of the intervention of one year or more.

Exclusion criteria

- We excluded trials of people diagnosed with 'metabolic syndrome' because this is a special population that is not representative of people with just intermediate hyperglycaemia. Also, the composite of risk indicators such as elevated blood lipids, insulin resistance, obesity, and high blood pressure, which is termed 'metabolic syndrome' is of doubtful clinical usefulness and uncertain distinct disease entity. However, in case we identified trials investigating participants with any

definition of metabolic syndrome, we would have summarised some basic trial information in an additional table.

- We excluded trials evaluating participants with raised blood glucose levels because of other medical conditions or interventions, for example, polycystic ovary syndrome or use of glucocorticoids.

We aimed to include trials explicitly describing that a portion of the included participants had intermediate hyperglycaemia. We contacted the trial investigators in order to obtain separate data on the group with intermediate hyperglycaemia and planned to include these in the meta-analyses.

We planned to include trials in obese people and participants with previous gestational diabetes, if trial investigators described that the participants had intermediate hyperglycaemia.

We planned to initially include a trial even if it did not report one or more of our primary or secondary outcome measures in the publication. If a trial did not report any of our primary or secondary outcomes, we would have included this trial and contacted the corresponding trial author for supplementary data. If no additional data were available, we planned to present this trial in a supplementary table.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Incidence of T2DM
- Serious adverse events

Secondary outcomes

- Cardiovascular mortality
- Non-fatal myocardial infarction
- Non-fatal stroke
- Congestive heart failure
- Amputation of lower extremity
- Blindness or severe vision loss
- End-stage renal disease
- Non-serious adverse events
- Hypoglycaemia
- Health-related quality of life
- Time to progression to T2DM
- Measures of blood glucose control
- Socioeconomic effects
- Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, body mass index (BMI), body weight, and blood pressure

Method of outcome measurement

- All-cause mortality: defined as death from any cause
- Incidence of T2DM and time to progression to T2DM: defined according to diagnostic criteria valid at the time the diagnosis was established, using the standard criteria valid at the time of the trial commencing (e.g. [ADA 2010](#); [WHO 1998](#)). If necessary, we used the trial authors' definition of T2DM.
- Serious adverse events: defined according to the International Conference on Harmonization Guidelines as any event that

leads to death, that is life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, or any important medical event that may have had jeopardised the patient or required intervention to prevent it ([ICH 1997](#)), or as reported in trials.

- Cardiovascular mortality, non-fatal myocardial infarction, congestive heart failure, non-fatal stroke, amputation of lower extremity, blindness or severe vision loss, hypoglycaemia (mild, moderate, severe/serious): defined as reported in trials
- End-stage renal disease: defined as dialysis, renal transplantation, or death due to renal disease
- Non-serious adverse events: defined as the number of participants with any untoward medical occurrence not necessarily having a causal relationship with the intervention
- Health-related quality of life: defined as mental and physical health-related quality of life as separate domains and combined, evaluated by a validated instrument such as Short-Form 36
- Measures of blood glucose control: fasting blood glucose, blood glucose two hours after ingestion of 75 g glucose, and HbA1c measurements
- Socioeconomic effects: for example, costs of the intervention, absence from work, medication consumption
- Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, BMI, body weight in kg, and blood pressure (systolic and diastolic blood pressure)

Timing of outcome measurement

Trials measured the following outcomes at any time during the intervention and during follow-up: all-cause mortality, serious adverse events and non-serious adverse events.

Trials measured the following outcomes at the end of the intervention and at the end of follow-up: incidence of T2DM, cardiovascular mortality, non-fatal myocardial infarction, congestive heart failure, non-fatal stroke, amputation of lower extremity, blindness or severe vision loss, hypoglycaemia, end-stage renal disease, health-related quality of life, measures of blood glucose control, socioeconomic effects, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, BMI, body weight, and blood pressure.

Specification of key prognostic variables

- Age
- Gender
- Equity issues (access to health care, social determinants)
- Ethnicity
- Hypertension
- Cardiovascular disease
- Obesity
- Previous gestational diabetes

Search methods for identification of studies

Electronic searches

For this update, the search strategies were revised and tested against the included studies identified in the previous version of this review. Due to substantial revision of the search strategies the search was run again from inception of each database to 7

December 2017. We placed no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12), via Cochrane Register of Studies Online
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; and Ovid MEDLINE(R) <1946 to Present>
- Embase <1974 to 6 December 2017>
- ClinicalTrials.gov
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/)

For detailed search strategies, see [Appendix 1](#). We continuously applied an email alert service for MEDLINE via OvidSP to identify newly published trials using the search strategy detailed in [Appendix 1](#). We obtained evaluations of all relevant non-English articles.

Searching other resources

For the original version of this review ([Van de Laar 2006](#)), we tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, systematic reviews and meta-analyses. In addition we contacted authors of included trials and other experts to identify any additional information on the retrieved trials and if further trials existed that we might have missed. Similarly, we contacted manufacturers and patent holders (Bayer AG, Sanofi-Synthelabo, Pfizer, Takeda), in order to retrieve information on published and unpublished AGI trials.

For the updated review, we tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of relevant systematic reviews and meta-analyses.

Data collection and analysis

Selection of studies

Two review authors (SM and FL), independently scanned the abstract, title, or both of every record we retrieved in the literature searches to determine which trials should be assessed further. We investigated the full text of all potentially relevant articles. We resolved discrepancies through consensus or by recourse to a third review author (WG). We prepared a flow diagram of the number of trials identified and excluded at each stage in accordance with the PRISMA flow diagram of trial selection ([Liberati 2009](#)).

Data extraction and management

For trials that fulfilled the inclusion criteria, two review authors (SM and FL), independently extracted outcome data and assessed the risk of bias. One review author (SM), extracted key characteristics of participants and interventions and another (FL), checked them. We reported data on efficacy outcomes and adverse events using standard data extraction sheets from Cochrane Metabolic and Endocrine Disorders (CMED). We resolved any disagreements by discussion or, if required, by consultation with a third review author (WG). For details see [Characteristics of included studies](#); [Table 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#); [Appendix 13](#); [Appendix 14](#); [Appendix 15](#); [Appendix 16](#); [Appendix 17](#); [Appendix 18](#); [Appendix 19](#).

We planned to provide information about potentially relevant ongoing trials, including trial identifier, in the Characteristics of ongoing studies table. For each included trial we tried to retrieve the protocol. If not available from the search of the databases, reference screening or internet searches, we asked trial authors to provide a copy of the protocol. We entered predefined outcomes in a 'Matrix of trial endpoint (publications and trial documents)' (see [Appendix 8](#)).

We emailed all authors of the included trials to enquire whether they were willing to answer questions regarding their trials. We presented the results of this survey in 'Survey of trial investigators providing information on included trials' (see [Appendix 16](#)). We sought relevant missing information on the trial from the primary author(s) of the articles, if possible.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we maximised the information yield by collating all available data and used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, or multiple reports of a primary trial as secondary references under the primary reference of the included, ongoing, or excluded trial.

Data from clinical trials registers

If data of included trials were available as trial results in clinical trials registers such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted data. If there was a full publication of the trial, we collated and critically appraised all available data.

Assessment of risk of bias in included studies

Two review authors (SM and FL) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus, or by consultation with a third review author (WG). If adequate information was not available from the trial publication, trial protocol, or both we contacted trial authors for missing data on 'Risk of bias' items.

We used the Cochrane 'Risk of bias' assessment tool ([Higgins 2017](#)), assigning assessments of low, high, or unclear risk of bias (for details see [Appendix 2](#); [Appendix 3](#)). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein ([Higgins 2017](#)).

We considered the following to be self-reported outcomes.

- Non-serious adverse events
- Hypoglycaemia
- Health-related quality of life
- Measures of blood glucose control
- BMI, body weight

We considered the following outcomes to be investigator-assessed.

- All-cause mortality
- Incidence of T2DM
- Serious adverse events
- Cardiovascular mortality

- Non-fatal myocardial infarction
- Non-fatal stroke
- Congestive heart failure
- Amputation of lower extremity
- Blindness or severe vision loss
- End-stage renal disease
- Hypoglycaemia
- Time to progression to T2DM
- Measures of blood glucose control
- Socioeconomic effects
- BMI, body weight
- Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides

Risk of bias for a trial across outcomes

Some 'Risk of bias' domains, such as selection bias (sequence generation and allocation sequence concealment), affected the risk of bias across all outcome measures in a trial. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a trial. In case of high risk of selection bias, we excluded the trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome, that is, both trial-level entries and outcome-specific entries. We defined 'low' risk of bias as low risk of bias for all key domains, 'unclear' risk of bias as unclear risk of bias for one or more key domains, and 'high' risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These were our main summary assessments that we incorporated in our judgements about the quality of evidence in the 'Summary of findings' table(s). We defined 'low' risk of bias as most information coming from trials at low risk of bias, 'unclear' risk of bias as most information coming from trials at low or unclear risk of bias, and 'high' risk of bias as a sufficient proportion of information coming from trials at high risk of bias.

Measures of treatment effect

When at least two trials were available for a comparison of a given outcome, we expressed dichotomous data as risk ratio (RR) with 95% confidence intervals (CI). We expressed continuous data reported on the same scale as mean difference (MD) with 95% CIs. For trials addressing the same outcome but using different outcome measure scales, we planned to use standardised mean differences (SMD) with 95% CIs. We planned to calculate time-to-event data as hazard ratio (HR) with 95% CIs with the generic inverse variance method.

The scales measuring health-related quality of life may go in different directions. Values in some scales increase with improved health-related quality of life, whereas in other scales, values decrease with improved health-related quality of life. To adjust for the different directions of the scales, we planned to multiply by -1 the scales that report better health-related quality of life with decreasing values.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we would have either combined groups to create a single pair-wise comparison or appropriately reduced the sample size so that the same participants did not contribute more than once (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Deeks 2017).

We planned to re-analyse cluster-randomised trials that did not appropriately adjust for potential clustering of participants within clusters in their analyses. We planned to use a design effect (DEFF), to inflate the variance of the intervention effects. Calculation of a DEFF involves estimation of an intra-cluster correlation (ICC) and the cluster size. We planned to obtain estimates of ICCs through contact with trial authors, or impute ICCs using estimates from other included trials that reported ICCs, or use external estimates from empirical research (e.g. Bell 2013). We planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

We tried to obtain missing data from trial authors and we carefully evaluated important numerical data such as screened, randomly-assigned participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations. If the publication did not explicitly mention that they used ITT analysis, we looked at the number of participants that they had randomised and the number of participants that they had analysed, and whether these numbers were equal.

We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and imputation methods (e.g. last observation carried forward).

We converted standard errors and CIs to standard deviations (SD) (Deeks 2017). When no differences in means and SDs were reported from baseline, we used the end-of follow-up values (Deeks 2017). Where means and SDs for outcomes were not reported and we did not receive the information we needed from trial authors, we calculated the SDs from standard errors, if possible. Otherwise we would have imputed the values by assuming the SDs of the missing outcome to be the average of the SDs from the trials that reported this information.

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency), by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I² statistic, which quantifies inconsistency

across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we found heterogeneity, we attempted to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we included 10 or more trials investigating a particular outcome, we planned to use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. Therefore, we planned to interpret results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display), a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration to the whole distribution of effects and presented a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events, such as event rates below 1%, we planned to use the Peto's odds ratio method, provided that there was no substantial imbalance between intervention and comparator group sizes and intervention effects were not exceptionally large. In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out the following subgroup analyses with investigation of interactions, as long as the size of the subgroups allowed it.

- Type of AGI
- Trials with long duration (two years or longer), versus trials with shorter duration (less than two years)
- Diagnostic criteria (IFG, IGT, HbA1c)
- Age, depending on data
- Gender
- Ethnicity, depending on data
- Comorbid conditions, such as hypertension, obesity, or both
- Participants with previous gestational diabetes mellitus
- AGI dose (up to the recommended dose for a glucose-lowering effect in people with T2DM versus higher doses)

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable), on effect sizes by restricting analysis to the following.

- Published trials
- Taking into account risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section
- Very long or large trials, to establish the extent to which they dominated the results
- Trials using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country

GRADE and certainty of the evidence

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results. Two review authors (SM and FL), independently rated the certainty of evidence for each outcome. We resolved any differences in assessment by discussion or by consulting a third review author (WG).

We included an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we planned to use the GRADEpro Guideline Development Tool (GDT) software, and planned to present evidence profile tables as an appendix (GRADEproGDT 2015). We presented results for the outcomes as described in the [Types of outcome measures](#) section. If meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of evidence using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review where necessary.

'Summary of findings' table

We presented a summary of the evidence in the 'Summary of findings' tables. These provide key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' tables based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017) using Review Manager 5 (RevMan 5) table editor (RevMan 2014). We reported the following outcomes, listed according to priority.

- All-cause mortality
- Incidence of T2DM
- Serious adverse events
- Cardiovascular mortality
- Non-fatal myocardial infarction/stroke and congestive heart failure
- Health-related quality of life
- Socioeconomic effects

RESULTS

Description of studies

For a detailed description of trials, see the [Table 1, Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of studies awaiting classification](#) sections.

Results of the search

The search is up to date as of December 2017. The search performed for the update of this review yielded 1237 records after duplicates were removed. We screened the title and abstract of these 1237

records and excluded 1212 on the basis that they were not relevant. After screening the full texts, we included five new trials. The search also included the publication of the 'Dutch acarbose intervention study in persons with impaired glucose tolerance trial' ([DAISI 2008](#)). We included this trial in the previous version of the review, even though at the full paper had not been published at the time.

The five new trials ([ABC 2017](#); [ACE 2017](#); [Kawamori 2009](#); [Koyasu 2010](#); [Yun 2016](#)), together with the five trials from the previous version of the review ([DAISI 2008](#); [EDIT 1997](#); [Fang 2004](#); [STOP-NIDDM 2002](#); [Wang 2000](#)), resulted in a total of 10 trials that we included in our systematic review. The study flow diagram is presented in [Figure 1](#).

Figure 1. Trial flow diagram

Included studies

A detailed description of the characteristics of included trials is presented elsewhere (see [Characteristics of included studies](#); [Table 1](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#); [Appendix 13](#); [Appendix 14](#); [Appendix 15](#)). The following is a succinct overview.

We have used an abbreviation of the trial name as the identifier for several included trials, namely the 'Dutch acarbose intervention study in persons with impaired glucose tolerance' ([DAISI 2008](#)), the 'Alpha-glucosidase-inhibitor blocks cardiac events in people with myocardial infarction and impaired glucose tolerance trial' ([ABC 2017](#)), the 'Acarbose cardiovascular evaluation trial' ([ACE 2017](#)), the

'Study to prevent non-insulin-dependent diabetes mellitus' (STOP-NIDDM 2002), and the 'Early diabetes intervention trial' (EDIT 1997).

Source of data

Nine trials were (predominantly) published as journal articles (ABC 2017; ACE 2017; DAISI 2008; Fang 2004; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002; Wang 2000; Yun 2016). For STOP-NIDDM 2002, we also considered additional data that we received from the trial authors in reply to specific questions from us, the STOP-NIDDM website, additional PowerPoint presentations, and debate articles as a result of the main publications. For DAISI 2008, we also used the statistical report. For the ABC 2017 and ACE 2017, we used additional data that we received from the trial authors. One trial was published on a website and as abstracts only (EDIT 1997).

Most trials were two-arm trials (ABC 2017; ACE 2017; DAISI 2008; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002; Wang 2000; Yun 2016). Two trials had multiple trial arms (EDIT 1997; Fang 2004).

Comparisons

Three trials compared the AGI acarbose to placebo (ACE 2017; DAISI 2008; STOP-NIDDM 2002). A further three trials compared acarbose to no intervention (Koyasu 2010; Wang 2000; Yun 2016). One trial compared acarbose to three other groups, namely placebo, metformin, and acarbose plus metformin (EDIT 1997). Another trial compared acarbose to three control groups, namely no intervention, metformin, and diet plus exercise (Fang 2004). Finally, one trial compared the AGI voglibose to placebo (Kawamori 2009) and one trial compared voglibose to diet and exercise (ABC 2017). We did not find any trials investigating miglitol.

Overview of trial populations

The 10 trials randomised 11,814 participants (Table 1). Of these, 5721 were randomised to an intervention group and 6093 to a comparator group. The percentage of participants that finished the trial in the intervention groups ranged between 50% and 99%. In the comparator groups, this ranged between 62% and 100%. Individual trial sample size ranged from 61 to 6522 participants.

Trial design

One trial had a 2x2 factorial design (EDIT 1997). The participants were first randomised to either acarbose or a matching placebo, and then also randomised to either metformin or a matching placebo. This resulted in four groups: acarbose plus metformin, acarbose plus placebo, metformin plus placebo, and placebo plus placebo. The other nine trials had a parallel design. All 10 trials had a superiority design.

Five trials compared the intervention to placebo (ACE 2017; DAISI 2008; EDIT 1997; Kawamori 2009; STOP-NIDDM 2002). Two trials compared the intervention to metformin (EDIT 1997; Fang 2004). Another two trials compared the intervention to diet and exercise (ABC 2017; Fang 2004). Four trials compared the intervention to no intervention (Fang 2004; Koyasu 2010; Wang 2000; Yun 2016).

Six trials were multicentre trials, with the number of centres ranging from 2 to 176 (ABC 2017; ACE 2017; EDIT 1997; Kawamori 2009; STOP-NIDDM 2002; Yun 2016).

Five trials were double-blinded for participants and personnel (ACE 2017; DAISI 2008; EDIT 1997; Kawamori 2009; STOP-NIDDM 2002).

Four trials were not blinded (ABC 2017; Koyasu 2010; Wang 2000; Yun 2016). One trial did not describe the method of blinding (Fang 2004).

Five trials blinded the outcome assessors (ABC 2017; ACE 2017; Koyasu 2010; DAISI 2008; STOP-NIDDM 2002). It was unclear whether the other trials blinded outcome assessors.

The trials were performed between 1995 and 2016. The duration of the follow-up ranged from one to six years. In two trials the intervention period was followed by a wash-out period. This was three months for STOP-NIDDM 2002 and four weeks for Kawamori 2009. In all other trials the intervention period and follow-up period were identical.

Four trials had a run-in period (ACE 2017; DAISI 2008; Kawamori 2009; STOP-NIDDM 2002). One trial was terminated earlier than planned because the interim analysis already showed the efficacy of the intervention (Kawamori 2009). Another trial was terminated early because the interim futility analysis showed an absence of beneficial treatment effect of voglibose compared to the control (ABC 2017).

Settings

STOP-NIDDM 2002 and Kawamori 2009, mainly recruited participants through screening of high-risk people (particularly first-degree relatives of people with diabetes), and followed them up as outpatients in trial centres.

DAISI 2008 recruited participants from the population register of the city of Hoorn and followed them up as outpatients in the trial centre. Koyasu 2010, recruited participants from patients admitted to the hospital for elective coronary angiography and followed them up as outpatients. Yun 2016 recruited participants from patients who were hospitalised for acute coronary syndrome and followed them up as outpatients. ACE 2017 invited patients at cardiovascular and endocrinology centres with coronary heart disease to attend a screening. In EDIT 1997, the participants were 'self-referred' but the exact setting is unclear. Setting and recruitment for the other three trials are also unclear (ABC 2017; Fang 2004; Wang 2000).

Participants

Four trials were performed in China (ACE 2017; Fang 2004; Wang 2000; Yun 2016), three in Japan (ABC 2017; Kawamori 2009; Koyasu 2010), one in the Netherlands (DAISI 2008), one in the UK (EDIT 1997), and one in multiple countries, namely Canada, Germany, Austria, the Nordic countries, Israel, and Spain (STOP-NIDDM 2002).

Three trials reported the ethnicity of the participants. In two of these trials, the participants were almost exclusively white (EDIT 1997; STOP-NIDDM 2002). In the other trial, the participants were almost entirely Han Chinese (ACE 2017). The percentage of female participants ranged from 8% to 52%. The mean age ranged from 47 years to 66 years. At baseline, the mean HbA1c ranged from 5.4% to 7.5%, the mean fasting plasma glucose (FPG) ranged from 5.5 to 6.6 mmol/L, and the mean two-hour post glucose (2hPG) ranged from 6.3 to 10.7 mmol/L. Lastly, the mean BMI at baseline ranged from 21 to 31 kg/m².

Five trials reported both comorbidities and comedications (ABC 2017; ACE 2017; Koyasu 2010; STOP-NIDDM 2002; Yun 2016). One

trial reported only comorbidities (Kawamori 2009). The most commonly reported comorbidities were hypertension and previous myocardial infarction. The most commonly used medications were beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and statins. In the ABC 2017 trial, considerably more people in the voglibose group used anti-platelet therapy at baseline than in the control group (96.5% and 92.5%, respectively).

In most trials, IGT was newly diagnosed (ACE 2017; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002; Wang 2000; Yun 2016). In three trials, this was not clearly stated (ABC 2017; EDIT 1997; Fang 2004).

The most common exclusion criterion was liver and/or kidney impairment (ABC 2017; ACE 2017; DAISI 2008; Koyasu 2010; STOP-NIDDM 2002; Yun 2016). Four trials excluded people with gastrointestinal problems (ACE 2017; DAISI 2008; Koyasu 2010; Yun 2016). Three trials excluded people with a history of diabetes (ACE 2017; Koyasu 2010; Yun 2016). Furthermore, three trials excluded women who were pregnant or planned to become pregnant, and people with an intolerance or sensitivity to AGI (ACE 2017; DAISI 2008; Koyasu 2010). Finally, five trials excluded participants with a recent cardiovascular event (ABC 2017; ACE 2017; DAISI 2008; Koyasu 2010; STOP-NIDDM 2002). There were also four trials that specifically included participants with a history of cardiovascular disease (CVD; ABC 2017; ACE 2017; Yun 2016; Koyasu 2010). This includes a history of myocardial infarction (ABC 2017), acute coronary syndrome, myocardial infarction, or (un)stable angina pectoris (ACE 2017), coronary artery disease or stable angina pectoris (Koyasu 2010), and acute coronary syndrome (Yun 2016). Three of these trials also excluded participants with a recent cardiovascular event (ABC 2017; ACE 2017; Koyasu 2010), as these trials wanted to include participants with a history of CVD, but who had not had an event recently. Because certain trials excluded participants with a history of CVD and other trials specifically included participants with a history of CVD, there is a different baseline risk for CVD between these trials.

EDIT 1997 intended to include people 'at risk of developing diabetes' with a FPG of 5.5 to 7.7 mmol/L. Based on the HbA1c and 2hPG baseline values, 36.9% of the participants had normal glucose tolerance, 8.1% had IFG, 25.5% had IGT, 14% had both IFG and IGT, and 15.5% had T2DM.

Diagnostic criteria

Four trials used the WHO 1985 criteria (WHO 1985), for IGT (a FPG of < 7.8 mmol/L and a 2hPG of 7.8 to 11.1 mmol/L; DAISI 2008; Fang 2004; STOP-NIDDM 2002; Wang 2000). However, DAISI 2008 increased the lower limit of the 2hPG measurement to 8.6 mmol/L, because of the higher incidence of conversion to diabetes. And STOP-NIDDM 2002 added a lower limit to the criteria of FPG, namely 5.6 mmol/L.

In 1998, the WHO changed the criteria for IGT to a FPG of less than 7.0 mmol/L and a 2hPG of 7.8 to 11.1 mmol/L (WHO 1998). Five trials included participants with IGT according to these criteria (ABC 2017; ACE 2017; Kawamori 2009; Koyasu 2010; Yun 2016). But again, some trials altered the criteria. Two trials lowered the FPG; Kawamori 2009 lowered it to 6.9 mmol/L and Yun 2016 lowered it to 6.1 mmol/L.

We excluded trials with participants that had T2DM. However, Koyasu 2010 also included participants with 'mild T2DM', which they defined as a FPG of less than 7.0 mmol/L, a 2hPG of more than 11.1 mmol/L, and a HbA1c of less than 6.5%. The current criteria for T2DM are a FPG of at least 7.0 mmol/L, or a 2hPG of at least 11.1 mmol/L (WHO/IDF 2006), or a HbA1c of at least 6.5% (ADA 2010). The 'mild T2DM' participants had a lower FPG and HbA1c than needed for a T2DM diagnosis, but did have a 2hPG of 11.1 or higher mmol/L. Therefore, the participants could be said to have T2DM. However, as the average 2hPG of the entire trial population was around 10.7 mmol/L in the acarbose group and 10.4 mmol/L in the control group, which is below the 11.1 mmol/L needed for T2DM diagnosis, and the participants had a FPG of 7.0 mmol/L or less and HbA1c of 6.5% or less, we decided to include this trial.

EDIT 1997 included participants at increased risk for T2DM with a FPG of 5.5 to 7.7 mmol/L.

Interventions

The alpha-glucosidase inhibitor interventions were all administered orally.

In two trials, the acarbose dose started at 25 mg three times a day and increased to 50 mg three times a day during the first weeks (Fang 2004; Yun 2016). In four trials, the acarbose dose was 50 mg three times a day from the start (ACE 2017; EDIT 1997; Koyasu 2010; Wang 2000). In DAISI 2008, the acarbose dose started at 50 mg once daily and increased to 50 mg three times a day. In STOP-NIDDM 2002, the acarbose dose started at 50 mg three times a day and ended at 100 mg three times a day or the maximum tolerated dose.

Finally, the two trials that investigated the effect of voglibose used a dose of 0.2 mg three times a day (ABC 2017; Kawamori 2009). ABC 2017 reduced the dose to a quarter or half of the original dose in case of gastrointestinal adverse effects.

In three trials, the participants did not take the trial medication on the days the glycaemic tests were performed (ACE 2017; DAISI 2008; Fang 2004). In one trial, the trialists describe that at the end of the intervention period the participants in the acarbose group took the final oral glucose tolerance test (OGTT) after a week-long wash-out period (Wang 2000). The other trials did not explicitly state if the participants were on trial medication or not when they performed the glycaemic tests (ABC 2017; EDIT 1997; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002; Yun 2016). However, for the FPG test the participants would have to have been fasting, and because the medications have to be taken with a meal, it can be assumed that they would not have taken their medication for these tests. Additionally, the medication would not have had an effect on the 2hPG OGTT tests. Alpha-glucosidase inhibitors inhibit an enzyme that breaks down complex carbohydrates, but the OGTT test uses glucose, a monosaccharide. The medication would only have had an effect if any of the trials had used a full-meal tolerance test, but this is not the case.

Outcomes

Six trials explicitly stated a primary and secondary outcome in the publication (ABC 2017; ACE 2017; DAISI 2008; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002). The most commonly defined primary outcome was the development of T2DM. ACE 2017 defined T2DM as two successive plasma glucose values of a FPG of 7.0 mmol/L, or more, or 2hPG of 11.1 mmol/L or more. Kawamori 2009

defined it as an HbA1c level of 6.5% or more and, on two separate occasions, a 2hPG of 11.1 mmol/L or more, a FPG of 7.0 mmol/L or more, or a random plasma glucose concentration of 11.1 mmol/L or more. [DAISI 2008](#), [Fang 2004](#) and [Wang 2000](#) defined T2DM as a FPG of 7.8 mmol/L or more, or a 2hPG of 11.1 mmol/L or more, or both. Finally, [STOP-NIDDM 2002](#) defined T2DM as a 2hPG of 11.1 mmol/L or more.

Trial registers or similar documents were not available for a number of trials ([EDIT 1997](#); [Fang 2004](#); [Wang 2000](#); [Yun 2016](#)). For [DAISI 2008](#) and [Kawamori 2009](#), there were no differences between the trial registers and the publications. However, for [STOP-NIDDM 2002](#), the definition of the outcome cardiovascular events was different in the final publication compared with the trial register information. In [ABC 2017](#), the outcome progression from IGT to T2DM, which was mentioned in the trial register, was not reported in the final publication. The trial register for [Koyasu 2010](#) mentions both the incidence of cardiovascular events and carotid intima-medial thickness (IMT) as primary outcome, but the publication only mentions the change in IMT.

Six trials reported all-cause mortality ([ABC 2017](#); [ACE 2017](#); [DAISI 2008](#); [Kawamori 2009](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#)). Four trials reported cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and congestive heart failure ([ABC 2017](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#); [Yun 2016](#)). Three trials reported serious adverse events ([ACE 2017](#); [DAISI 2008](#); [Kawamori 2009](#)). Four trials reported non-serious adverse events ([DAISI 2008](#); [Kawamori 2009](#); [STOP-NIDDM 2002](#); [Wang 2000](#)).

Of the secondary outcomes, seven trials reported measures of blood glucose control and lipids ([ABC 2017](#); [ACE 2017](#); [DAISI 2008](#); [Fang 2004](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#); [Yun 2016](#)). Three trials reported body weight ([ACE 2017](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#)), and five listed reported BMI ([ACE 2017](#); [Fang 2004](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#); [Yun 2016](#)). Six trials reported data on blood pressure ([ABC 2017](#); [ACE 2017](#); [Fang 2004](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#); [Yun 2016](#)). Finally, one trial reported hypoglycaemic episodes ([ACE 2017](#)). [EDIT 1997](#) reported that they had investigated a number of outcomes (e.g. plasma glucose and lipids), but these data have not been accessible to us thus far. We acquired some of the data on measures of blood glucose control, lipids, body weight, BMI, and blood pressure through contact with the trial authors ([ABC 2017](#); [ACE 2017](#); [STOP-NIDDM 2002](#)), or from the trial protocol ([DAISI 2008](#)).

Subgroup analyses within the included trials

The subgroup analyses in [ACE 2017](#) looked at sex (male/female), region in China (Beijing and Tainjin/Central/South and Southwest/West and East/Northeast/Hong Kong), coronary heart disease inclusion criteria (previous myocardial infarction/previous unstable angina/current stable angina/more than 1 of the above), history of heart failure (yes/no), age (≤ 63.5 / > 63.5), HbA1c (≤ 5.9 / > 5.9), FPG (≤ 5.47 mmol/L/ > 5.47 mmol/L), 2hPG (≤ 9.12 mmol/L/ > 9.12 mmol/L), systolic blood pressure (≤ 130 mmHg/ > 130 mmHg), BMI (≤ 25 kg/m²/ > 25 kg/m²), and estimated glomerular filtration rate (≤ 88.5 mL/min/1.73 m²/ > 25.0 mL/min/1.73 m²). They found a HR of 0.70 (95% CI 0.50 to 0.99) for the 5-point composite outcome for the subgroup of the northeast region of China. There were no statistically significant effects found in the other subgroups.

The subgroups that [ABC 2017](#) analysed were sex (male/female), age (< 65 / ≥ 65), BMI (< 25 kg/m²/ ≥ 25 kg/m²), hypertension (no/yes), dyslipidaemia (no/yes), smoking (no/yes), arteriosclerosis obliterans (no/yes), and OGTT (no/yes). The only factor that statistically significantly affected the risk of cardiovascular events was age. The group of less than 65 years had statistically significantly fewer events in the control group than in the voglibose group (logrank $P = 0.02$).

In [Kawamori 2009](#), the analysed subgroups were age (10-year increase), sex (male/female), BMI (5 kg/m² increase), dyslipidaemia (yes/no), hypertension (yes/no), family history of diabetes (yes/no), 2hPG (0.55 mmol/L increase), insulinogenic index (0.2 decrease), homoeostasis model assessment for insulin resistance (1 increase), smoker (yes/no), intensity of daily activity (I/III to IV), intensity of daily activity (II/III to IV), and concomitant use of ACE inhibitor or angiotensin II receptor blocker (yes/no). According to these subgroup analyses, people with a higher BMI (HR 1.495, $P = 0.0023$), people with a lower insulinogenic index (HR 1.246, $P < 0.0001$), and people who had a higher intensity of daily activity (HR 1.992, $P < 0.0001$), had a higher risk of developing T2DM.

In [STOP-NIDDM 2002](#), the (univariate) subgroup analyses included FPG, 2hPG, fasting insulin, 2-hour insulin, HbA1c, total cholesterol, LDL, HDL, total triglycerides, systolic blood pressure, diastolic blood pressure, weight, BMI, waist circumference, concomitant medications, and current smoker status. People with a higher FPG (HR 1.767, $P = 0.03$), people with a higher systolic blood pressure (HR 1.029, $P < 0.001$), people with a higher diastolic blood pressure (HR 1.043, $P = 0.006$), and people with concomitant medications (HR 2.071, $P = 0.02$) had a higher risk of cardiovascular events. They also performed multivariate analyses on the outcomes FPG (HR 1.830, $P = 0.03$) and systolic blood pressure (HR 1.031, $P < 0.001$).

Excluded studies

We excluded 1212 records after screening the title and abstract. We read the full text of the remaining 25 records. We excluded one trial after evaluation of the full publication, because the population consisted of both people with T2DM and people with IGT ([Kataoka 2012](#)). We contacted the trial authors for data for people with IGT only, but did not receive a reply. The other excluded records were not full-text publications, but full-text online trial records. Six of these trials had a trial population (T2DM) that did not match our criteria ([ABDOMEN study](#); [Aoki 2010](#); [MM study](#); [Narita 2009](#); [Toyoda 2012](#); [Watada 2012](#)), and three trials were never completed ([JEDIS study](#); [Medizinische Klinik B study](#); [NCT00417950](#)). There are a further three trials that we excluded after evaluation of the full publication at the time of the original version of this review ([EDIP](#); [Mangiagli 2004](#); [Yang 2001](#)). We excluded these trials due to the participants having T2DM ([EDIP](#)), no randomisation ([Mangiagli 2004](#)) and no mention of randomisation ([Yang 2001](#)).

Risk of bias in included studies

For details on the risk of bias of the included trials see [Characteristics of included studies](#).

For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials see [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials (blank cells indicate that the particular outcome was not measured in some trials). T2DM: type 2 diabetes mellitus

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial (blank cells indicate that the particular outcome was not measured in some trials) ABC: Alpha-glucosidase-inhiT2DM: type 2 diabetes mellitus

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): all-cause/cardiovascular mortality	Blinding of participants and personnel (performance bias): amputation, blindness/severe vision loss, end-stage renal disease	Blinding of participants and personnel (performance bias): health-related quality of life	Blinding of participants and personnel (performance bias): hypoglycaemia	Blinding of participants and personnel (performance bias): incidence of T2DM	Blinding of participants and personnel (performance bias): measures of blood glucose control	Blinding of participants and personnel (performance bias): non-fatal myocardial infarction/stroke, congestive heart failure	Blinding of participants and personnel (performance bias): non-serious adverse events	Blinding of participants and personnel (performance bias): serious adverse events	Blinding of participants and personnel (performance bias): socioeconomic effects	Blinding of participants and personnel (performance bias): time to progression to T2DM	Blinding of outcome assessment (detection bias): all-cause/cardiovascular mortality	Blinding of outcome assessment (detection bias): amputation, blindness/severe vision loss, end-stage renal disease	Blinding of outcome assessment (detection bias): health-related quality of life	Blinding of outcome assessment (detection bias): hypoglycaemia	Blinding of outcome assessment (detection bias): incidence of T2DM	Blinding of outcome assessment (detection bias): measures of blood glucose control	Blinding of outcome assessment (detection bias): non-fatal myocardial infarction/stroke, congestive heart failure	Blinding of outcome assessment (detection bias): non-serious adverse events	Blinding of outcome assessment (detection bias): serious adverse events	Blinding of outcome assessment (detection bias): socioeconomic effects	Blinding of outcome assessment (detection bias): time to progression to T2DM	Incomplete outcome data (attrition bias): all-cause/cardiovascular mortality	Incomplete outcome data (attrition bias): amputation, blindness/severe vision loss, end-stage renal disease	Incomplete outcome data (attrition bias): health-related quality of life	Incomplete outcome data (attrition bias): hypoglycaemia	Incomplete outcome data (attrition bias): incidence of T2DM	Incomplete outcome data (attrition bias): measures of blood glucose control	Incomplete outcome data (attrition bias): non-fatal myocardial infarction/stroke, congestive heart failure	Incomplete outcome data (attrition bias): non-serious adverse events	Incomplete outcome data (attrition bias): serious adverse events	Incomplete outcome data (attrition bias): socioeconomic effects	Incomplete outcome data (attrition bias): time to progression to T2DM	Selective reporting (reporting bias)	Other bias				
ABC 2017	●	●	●																																				●	●	
ACE 2017	●	●	●			●		●	●	●	●			●						●	●	●	●			●														●	●
DAISI 2008	●	●	●					●	●	●	●			●						●	●	●	●			●														●	?
EDIT 1997	?	?			?			●	●		?									●	●								?											●	?
Fang 2004	?	?	●					●	●					●						●	●					●													?	●	
Kawamori 2009	●	●	●					●	●		●	●								●	●					●														●	●
Koyasu 2010	?	?	●					●	●					●						●	●					●														●	?
STOP-NIDDM 2002	●	●	●					●	●	●	●			●						●	●	●	●			●														●	?
Wang 2000	?	?						●			●									●																				?	●
Yun 2016	●	?	●					●	●	●	●			●						●	●					●														?	●

Allocation

With respect to selection bias, five trials had both an adequate randomisation and allocation concealment (ABC 2017; ACE 2017; Kawamori 2009; DAISI 2008; STOP-NIDDM 2002). The risk of selection bias was unclear for the other trials. Fang 2004 used the 'random number table method', however, there was baseline imbalance (e.g. a 2hPG of 8.38 mmol/L in the acarbose group and a 2hPG of 6.35 mmol/L in the no-intervention group), which suggests the randomisation was not adequate.

Blinding

Four trials reported blinding of participants and personnel (ACE 2017; DAISI 2008; Kawamori 2009; STOP-NIDDM 2002). Four trials had no blinding of participants and personnel (ABC 2017; Koyasu 2010; Wang 2000; Yun 2016), and for two trials information was lacking about precise methods of blinding (EDIT 1997; Fang 2004). Five trials assessed outcomes in a blinded fashion (ABC 2017; ACE 2017; DAISI 2008; Koyasu 2010; STOP-NIDDM 2002). In the other trials, this was unclear.

We judged the risk of performance and detection bias as low for the following outcomes: all-cause mortality, cardiovascular mortality, incidence of T2DM, measures of blood glucose control, serious adverse events, amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, hypoglycaemia, time to progression of T2DM, socioeconomic effects, lipids, BMI, body weight, and blood pressure because we judged these outcomes were not likely to have been influenced by blinding conditions. Only EDIT 1997 measured the outcome health-related quality of life, and the risk of performance and detection bias was unclear, because there was not enough information available.

The outcome non-serious adverse events had a low risk of performance bias in trials with adequate blinding (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), an unclear risk of bias in one trial (EDIT 1997), and a high risk of bias in the trials with no blinding (Yun 2016; Wang 2000). The risk of detection bias for this outcome was low in two trials (DAISI 2008; STOP-NIDDM 2002), and unclear in four trials (Fang 2004; Kawamori 2009; Wang 2000; Yun 2016).

Incomplete outcome data

The outcomes all-cause mortality and cardiovascular mortality had a high risk of attrition bias in three trials (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), and a low risk in four trials (ABC 2017; ACE 2017; Koyasu 2010; Yun 2016). The incidence of T2DM had high risk of attrition bias in three trials (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), an unclear risk in one trial (EDIT 1997), and a low risk in three trials (ACE 2017; Fang 2004; Wang 2000). The outcome measures of blood glucose control had a high risk of attrition bias in three trials (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), an unclear risk in one trial (EDIT 1997), and a low risk in three trials (Fang 2004; Koyasu 2010; Wang 2000). The outcome non-fatal myocardial infarction had a high risk of attrition bias in one trial (STOP-NIDDM 2002), and a low risk in three trials (ABC 2017; Koyasu 2010; Yun 2016). The outcome non-serious adverse events had a high risk of attrition bias in three trials (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), an unclear risk in one trial (EDIT 1997), and a low risk in three trials (ACE 2017; Wang 2000; Yun 2016). Finally, the outcome serious adverse events had a high risk of attrition bias in two trials (DAISI 2008; Kawamori 2009) and a low risk in three trials (ACE 2017; Wang 2000; Yun 2016).

All trials had losses to follow-up. The dropout rate ranged from 5.9% to 50%.

The overall risk of attrition bias was high in three trials (DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), especially due to a high number of dropouts and a high difference in attrition rate between groups. DAISI 2008 had the highest percentage of dropouts, with a 50% dropout in the treatment group and 47.9% in the control group. STOP-NIDDM 2002 also had quite a high number of dropouts, with a much higher dropout rate in the treatment group (30.9%), compared to the control group (19%). Most dropouts in the intervention groups were due to adverse events, in particular gastrointestinal adverse effects. In the control groups, the most common dropout reason was withdrawn consent (STOP-NIDDM 2002), or adverse events (DAISI 2008; Kawamori 2009). In one trial, the risk of attrition bias was unclear (EDIT 1997), and in the remaining trials, the risk was low (Fang 2004; Koyasu 2010; Wang 2000; Yun 2016). Five trials analysed the data using intention-to-treat analysis (ABC 2017; ACE 2017; DAISI 2008; Kawamori 2009; STOP-NIDDM 2002), though in the case of STOP-NIDDM 2002 they used a so-called "modified intention-to-treat analysis", where trialists excluded 61 participants who dropped out immediately after randomisation without taking trial medication.

Selective reporting

For three trials, the risk of reporting bias was unclear, due to the fact that there was no protocol or trials register available (Fang 2004; Wang 2000; Yun 2016). The risk of reporting bias was low in two trials (ACE 2017; DAISI 2008). The outcomes specified in DAISI 2008 were the same as specified in the trials register and the publication. ACE 2017 showed a difference between the trials register and the final publication regarding the primary composite outcome (a three-point major cardiovascular adverse event outcome), which was changed into a five-point major cardiovascular adverse event outcome, which we did not judge as a high risk of reporting bias.

For five trials, the risk of reporting bias was high (ABC 2017; EDIT 1997; Kawamori 2009; Koyasu 2010; STOP-NIDDM 2002). In their trial registration, the ABC 2017 authors describe the primary outcomes as cardiovascular mortality and cardiovascular

events. However, in the final publication they specify these outcomes as, "cardiovascular death, non-fatal MI, non-fatal unstable angina, non-fatal stroke, and percutaneous coronary intervention/coronary artery bypass graft". Furthermore, the secondary outcomes mentioned in the trials register (all-cause mortality; hospitalisation due to heart failure, coronary artery disease, and cerebrovascular disease; progression of IGT to diabetes; development or deterioration of hypertension or hyperlipidaemia; deterioration of renal function), were different in the publication (all-cause mortality; hospitalisation due to heart failure; death from cardiovascular disease; non-fatal myocardial infarction; non-fatal unstable angina; treatment with coronary revascularisation; non-fatal stroke).

The trial register for Koyasu 2010 mentions the primary outcomes, incidence of cardiovascular events (defined as, "new onset myocardial infarction, worsening anginal status and/or angiographic restenosis"), and carotid intima-medial thickness (IMT). In the publication however, the only primary outcome is the change in IMT measured in the right and left common carotid arteries. Similarly, there are differences in the secondary outcomes. In the trial register, these are ultrasonic echocardiography measures, HbA1c, insulin resistance index (IRI), blood glucose levels, HOMA-R and HOMA-beta (homeostatic model assessment), and plasma lipid profile. In the publication, the secondary outcomes are changed to glucose profiles (OGTT), HbA1c and lipid profiles, incidence of death, non-fatal myocardial infarction, repeat percutaneous coronary intervention, and stroke. Thus, the ultrasonic echocardiography measures, IRI, HOMA-R and HOMA-beta are not mentioned, and mortality and cardiovascular events are added.

For the STOP-NIDDM 2002 trial, most outcomes were the same for the design paper (Chiasson 1998 under STOP-NIDDM 2002), and the publications (Chiasson 2002; Chiasson 2003 under STOP-NIDDM 2002). However, there was a difference in the definition of cardiovascular events. In the design paper this outcome included myocardial infarction, cerebrovascular accident and congestive heart failure. In the final publications trialists also included new angina, revascularisation procedures, cardiovascular death, and peripheral vascular disease. Kawamori 2009 measured outcomes, but not all the data were reported (FPG, HbA1c, triglycerides, total cholesterol, HDL-cholesterol, blood pressure, and body weight). EDIT 1997 had a high risk of reporting bias, due to the fact that this trial finished more than 10 years ago and has still not been published.

Other potential sources of bias

Three trials had an unclear risk of funding bias (DAISI 2008; EDIT 1997; STOP-NIDDM 2002). Four trials were funded by Bayer (ACE 2017; DAISI 2008; EDIT 1997; STOP-NIDDM 2002). One trial was additionally funded by Merck-Lipha (EDIT 1997), and two trials were funded by 'non-commercial' funding (ABC 2017; Kawamori 2009). Additionally, in ABC 2017, the main researchers received grants and personal fees from Pfizer and Takeda, and in ACE 2017, the main researcher received grants from Bayer.

Effects of interventions

See: [Summary of findings for the main comparison Acarbose compared to placebo](#); [Summary of findings 2 Acarbose compared to no intervention](#)

Most data for our analyses originated from trials comparing AGI with placebo (N = 4) or comparing AGI with no intervention (N = 4). Therefore, we presented 'Summary of findings' tables for these main comparisons ([Summary of findings for the main comparison](#); [Summary of findings 2](#)).

Baseline characteristics

For details of baseline characteristics, see [Appendix 5](#), [Appendix 6](#) and [Appendix 7](#).

Alpha-glucosidase inhibitors versus placebo

Four trials compared acarbose with placebo ([ACE 2017](#); [DAISI 2008](#); [EDIT 1997](#); [STOP-NIDDM 2002](#)). However, only three trials provided sufficient data to allow statistical comparison ([ACE 2017](#); [DAISI 2008](#); [STOP-NIDDM 2002](#)). One trial has not been published yet and most data are not available ([EDIT 1997](#)). One trial compared voglibose with placebo ([Kawamori 2009](#)).

None of the trials reported amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, health-related quality of life, time to progression to T2DM, or socioeconomic effects.

Primary outcomes

All-cause mortality

In the acarbose groups, 223 (5.5%) out of 4046 participants died, compared to 225 (5.6%) out of 4023 in the placebo groups (RR 0.98, 95% CI 0.82 to 1.18; P = 0.86; 3 trials; 8069 participants; very low-certainty evidence; [Analysis 1.1](#)). The 95% prediction interval ranged between 0.29 and 3.27. [ACE 2017](#), which included participants with coronary heart disease, contributed most weight to the analysis; 97.1% of the events occurred in this trial.

In the voglibose group, six (0.7%) out of 897 participants died, compared to no participants out of 881 in the placebo group (RR 12.77, 95% CI 0.72 to 226.31; P = 0.08; 1 trial; 1778 participants; very low-certainty evidence; [Analysis 1.1](#); [Kawamori 2009](#)).

Incidence of T2DM

In the acarbose groups 670 (16.7%) out of 4014 participants developed T2DM, compared to 812 (20.3%) out of 3994 in the placebo groups. Therefore, acarbose reduced or delayed the incidence of T2DM in the acarbose group: RR 0.82, 95% CI 0.75 to 0.89; P < 0.0001; 3 trials; 8008 participants; moderate-certainty evidence; [Analysis 1.2](#)). The 95% prediction interval ranged between 0.48 and 1.40. [ACE 2017](#), which included participants with coronary heart disease and IGT, weighed heavy in this analysis: 64.0% of cases occurred in this trial.

[ACE 2017](#) and [DAISI 2008](#) defined T2DM as two successive values of FPG of 7.0 mmol/L or more, and 2hPG of 11.1 mmol/L or more ([WHO 1985](#)). [STOP-NIDDM 2002](#) defined T2DM as a 2hPG of 11.1 mmol/L or more, based on one test.

[EDIT 1997](#) reported that the use of acarbose had a preventive effect on the incidence of T2DM for people with IGT (RR 0.66, P = 0.046). However, acarbose did not have a preventive effect when looking at the entire population consisting of people with IGT, IFG and NGT (RR 1.04, P = 0.81).

In the voglibose group, 50 (5.6%) out of 897 participants developed T2DM, compared to 106 (12%) out of 881 in the placebo group (RR 0.46, 95% CI 0.34 to 0.64; P < 0.0001; 1 trial; 1778 participants; low-certainty evidence; [Analysis 1.2](#); [Kawamori 2009](#)).

Serious adverse events

Three hundred and fifty-one (9.5%) out of 3324 participants in the acarbose groups experienced serious adverse events compared to 312 (9.5%) out of 3301 in the placebo groups (RR 1.12, 95% CI 0.97 to 1.29; P = 0.13; 2 trials; 6625 participants; low-certainty evidence; [Analysis 1.3](#)). [ACE 2017](#), which included participants with coronary heart disease and IGT weighed heavy in this analysis: 97.9% of the events occurred in this trial.

The [ACE 2017](#) authors did not report serious adverse events thought to be possible trial endpoints (i.e. cardiovascular events), and reported other serious adverse events if they occurred in at least 1% of participants in either treatment group. [DAISI 2008](#) reported all serious adverse events.

The most common serious adverse events in [ACE 2017](#) were benign tumours, malignant or unspecified neoplasms (85 (3%) in the acarbose group and 88 (2%) in the placebo group). In [DAISI 2008](#), the most common serious adverse events were cardiovascular events (3 (6.6%) in the acarbose group and 3 (5%) in the placebo group). [STOP-NIDDM 2002](#) reported 220 cases (31%) of cardiovascular adverse events in the acarbose group and 287 (40%) in the placebo group.

In the voglibose group, five (0.6%) out of 897 participants experienced serious adverse events compared to two (0.2%) out of 881 in the placebo group (RR 2.46, 95% CI 0.48 to 12.62; P = 0.28; 1 trial; 1778 participants; very low-certainty evidence; [Analysis 1.3](#); [Kawamori 2009](#)). These was a cerebral infarction and cholecystitis in the placebo group, and cholecystitis, colonic polyp or rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid haemorrhage in the voglibose group.

Neoplasms

[ACE 2017](#) reported that 88 participants in the placebo group (2%) and 85 participants in the acarbose group (3%) developed a benign tumour, malignant, or unspecified neoplasm. In [DAISI 2008](#), one participant in the acarbose group died from colon carcinoma eight months after the last intake of the medication (1.7%). In [STOP-NIDDM 2002](#) there were three deaths from cancer in the acarbose group (0.4%), and one in the placebo group (0.1%). Finally, in [Kawamori 2009](#) there was one death of cancer in the voglibose group (0.1%).

Secondary outcomes

Cardiovascular mortality

In the acarbose groups 148 (3.7%) out of 4046 participants died of cardiovascular causes, compared to 167 (4.2%) out of 4023 in the placebo group (RR 0.88, 95% CI 0.71 to 1.10; P = 0.26; 3 trials; 8069 participants; very low-certainty evidence; [Analysis 1.4](#)). The 95% prediction interval ranged between 0.21 and 3.74. [ACE 2017](#), which included participants with coronary heart disease, weighed heavy in this analysis: 97.8% of the events occurred in this trial.

[STOP-NIDDM 2002](#) defined cardiovascular mortality as, "death due to congestive heart failure, myocardial infarction, cerebrovascular

event, cardiovascular procedures, pulmonary embolism, or sudden death.” [ACE 2017](#) and [DAISI 2008](#) did not specifically define this outcome.

In the voglibose group one (0.1%) out of 897 participants experienced serious adverse events compared to 0 (0%) out of 881 in the placebo group (RR 2.95, 95% CI 0.12 to 72.23; $P = 0.51$; 1 trial; 1778 participants; very low-certainty evidence; [Analysis 1.4](#); [Kawamori 2009](#)).

Non-fatal myocardial infarction

In the acarbose group one (0.1%) out of 742 participants had a non-fatal myocardial infarction, compared to 15 (2%) out of 744 in the placebo group (RR 0.10 (95% CI 0.02 to 0.53); $P = 0.007$; 2 trials; 1486 participants; very low-certainty evidence; [Analysis 1.5](#)). [STOP-NIDDM 2002](#) defined non-fatal myocardial infarction as, “clinical symptoms of myocardial ischaemia with elevated serum cardiac enzymes and electrocardiographic changes; at least 2 of 3 criteria had to be present for the clinical diagnosis”. [DAISI 2008](#) did not specifically define the outcome.

[Kawamori 2009](#), the voglibose trial, did not report this outcome.

Non-fatal stroke

In the acarbose group, two (0.3%) out of 682 participants had a non-fatal stroke, compared to four (0.6%) out of 686 in the placebo group (RR 0.50, 95% CI 0.09 to 2.74; $P = 0.43$; 1 trial; 1368 participants; very low-certainty evidence; [Analysis 1.6](#)).

[Kawamori 2009](#), the voglibose trial, did not report this outcome.

Congestive heart failure

In the acarbose group, 65 (1.6%) out of 3954 participants had congestive heart failure, compared to 75 (1.9%) out of 3936 in the placebo group (RR 0.87, 95% CI 0.63 to 1.21; $P = 0.40$; 2 trials; 7890 participants; very low-certainty evidence; [Analysis 1.7](#)). [ACE 2017](#), which included participants with coronary heart disease, weighed heavy in this analysis: 98.6% of the events occurred in this trial.

[STOP-NIDDM 2002](#) defined congestive heart failure as, “recent onset of new or aggravation of symptoms compatible with heart failure with supportive documentation such as chest radiograph or electrocardiographic changes”. [ACE 2017](#) defined congestive heart failure as hospital admission for heart failure.

[Kawamori 2009](#), the voglibose trial, did not report this outcome.

Non-serious adverse events

In the acarbose group 751 (96.9%) out of 775 participants experienced non-serious adverse events, compared to 723 (93.3%) out of 775 in the placebo group (RR 1.04, 95% CI 1.01 to 1.06; $P = 0.0008$; 2 trials; 1550 participants; [Analysis 1.8](#)). [STOP-NIDDM 2002](#) weighed heaviest in this analysis, as it contributes more than 93% of the events.

[ACE 2017](#) only recorded non-serious adverse events, “when trial medication was reduced or stopped as a result, or the event was thought to be related to study medication” and if they occurred in at least 5% of either treatment group. The only reported non-serious adverse events were gastrointestinal disorders with 215 cases (7%) in the acarbose group and 150 cases (5%) in the placebo group. The most common non-serious adverse events in [DAISI 2008](#)

were digestive problems, with 37 (60.7%) in the acarbose group and 10 (16.7%) in the placebo group. [STOP-NIDDM 2002](#) also noted the frequency of gastrointestinal adverse events. There were 597 (83.6%) cases of gastrointestinal adverse events in the acarbose group and 426 (59.6%) in the placebo group.

In the voglibose group 805 (89.7%) out of 897 participants experienced non-serious adverse events, compared to 748 (84.9%) out of 881 in the placebo group (RR 1.06, 95% CI 1.02 to 1.10; $P = 0.002$; 1 trial; 1778 participants; [Analysis 1.8](#); [Kawamori 2009](#)). The most common non-serious adverse events were gastrointestinal problems, with 478 cases (53%) in the voglibose group and 200 cases (23%) in the placebo group.

Hypoglycaemia

In the acarbose group 421 (12.9%) out of 3272 participants experienced a hypoglycaemic episode, compared to 416 (12.8%) out of 3250 in the placebo group (RR 1.01, 95% CI 0.89 to 1.14; $P = 0.94$; 1 trial; 6522 participants; [Analysis 1.9](#); [ACE 2017](#)).

Measures of blood glucose control

Fasting plasma glucose

The mean difference (MD) in change in fasting plasma glucose for acarbose versus placebo was -0.07 mmol/L (95% CI -0.12 to -0.02 ; $P = 0.008$; 3 trials; 7368 participants; [Analysis 1.10](#)). The 95% prediction interval ranged between -0.39 mmol/L and 0.25 mmol/L.

[EDIT 1997](#) found that acarbose decreased fasting plasma glucose by 0.1 mmol/L ($P = 0.0043$).

2-hour plasma glucose concentrations (OGTT)

Acarbose decreased post-load glucose by 0.53 mmol/L (95% CI 0.14 to 0.92 ; $P = 0.008$; 3 trials; 6498 participants; [Analysis 1.11](#)). The 95% prediction interval ranged between -4.92 mmol/L and 3.86 mmol/L.

[EDIT 1997](#) found that acarbose decreased post-load blood glucose by 0.4 mmol/L ($P = 0.0075$).

HbA1c

The MD in HbA1c for acarbose versus placebo was -0.1% (95% CI -0.1 to -0.05 ; $P < 0.0001$; 3 trials; 6833 participants; [Analysis 1.12](#)). The 95% prediction interval ranged between -0.3% and 0.1% .

Plasma lipids

The MD in change in total cholesterol for acarbose versus placebo was -0.05 mmol/L (95% CI -0.10 to 0.00 ; $P = 0.06$; 3 trials; 6815 participants; [Analysis 1.13](#)). The 95% prediction interval ranged between -0.37 mmol/L and 0.27 mmol/L.

For change in HDL-cholesterol for acarbose versus placebo the MD was 0.01 mmol/L (95% CI -0.00 to 0.03 ; $P = 0.13$; 3 trials; 6807 participants; [Analysis 1.14](#)). The 95% prediction interval ranged between -0.12 mmol/L and 0.14 mmol/L.

The MD in change in LDL-cholesterol for acarbose versus placebo was -0.03 mmol/L (95% CI -0.07 to 0.01 ; $P = 0.11$; 3 trials; 6699 participants; [Analysis 1.15](#)). The 95% prediction interval ranged between -0.29 mmol/L and 0.23 mmol/L.

The MD in change in triglycerides for acarbose versus placebo was -0.07 mmol/L (95% CI -0.17 to 0.03 ; $P = 0.19$; 3 trials; 6843

participants; [Analysis 1.16](#)). The 95% prediction interval ranged between -0.78 mmol/L and 0.64 mmol/L.

Body weight

The MD in change in body weight for acarbose versus placebo was -0.7 kg (95% CI -1.6 to 0.2; $P = 0.14$; 2 trials; 6959; [Analysis 1.17](#)). Fixed-effect model analysis showed a difference of -0.4 kg, 95% CI -0.6 to -0.2; $P = 0.001$ in favour of acarbose.

For BMI, the MD was -0.2 kg/m², 95% CI -0.4 to 0.03; $P = 0.10$; 2 trials; 6953 participants; [Analysis 1.18](#). Fixed-effect model analysis showed a difference of -0.1 kg/m² (95% CI -0.2 to -0.04; $P = 0.003$), in favour of acarbose.

Blood pressure

The MD in change in diastolic blood pressure for acarbose versus placebo was -0.3 mmHg (95% CI -0.8 to 0.2; $P = 0.25$; 2 trials; 7452 participants; [Analysis 1.19](#)).

For systolic blood pressure the MD was -0.5 mmHg (95% CI -1.3 to 0.3; $P = 0.24$; 2 trials; 7452 participants; [Analysis 1.20](#)).

Adjustment for high discontinuation rate in the acarbose arm of STOP-NIDDM 2002

The discontinuation rate in the acarbose group of [STOP-NIDDM 2002](#) was higher than in the placebo group (acarbose 31% versus placebo 19%). Despite the fact that discontinuing participants remained in the ITT analyses, it is possible that those participants were not followed up regularly every third month, and thus possible occurrence of T2DM or a cardiovascular event was less likely to be discovered ([Sawicki 2004](#)).

In order to investigate the possible influence of differences in the frequency of follow-up, we re-analysed the data with the following adjustments: first we requested the mean number of trial visits for both treatment groups. Next, we divided the number of visits of the placebo group by the number of visits in the acarbose group. We used this outcome as a correction factor for the number of events in the acarbose group (occurrence of cardiovascular morbidity and T2DM).

The authors of [STOP-NIDDM 2002](#) reported that the mean numbers of trial visits in the acarbose group ($N = 682$) and in the placebo group ($N = 686$) were 13.3 (SD = 5.4) and 14.6 (SD = 4.3), respectively. The calculated correction factor was: $14.6/13.3 = 1.1$. The outcomes before and after this correction factor are listed in [Appendix 19](#). The effects sizes for incidence of T2DM and occurrence of any cardiovascular disease became smaller after the correction but remained statistically significant. The effects size for myocardial infarctions did not change (due to the fact that there was only one case in the acarbose group). The other outcomes remained statistically not significant after correction.

Alpha-glucosidase inhibitors versus metformin

Two trials ([EDIT 1997](#); [Fang 2004](#)), investigated this comparison but only [Fang 2004](#) provided data for our analyses.

[Fang 2004](#) did not report serious adverse events, cardiovascular mortality, non-fatal myocardial infarction, congestive heart failure, non-fatal stroke, amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, non-serious adverse

events, hypoglycaemia, health-related quality of life, time to progression to T2DM, or socioeconomic effects.

Primary outcomes

All-cause mortality

There were no deaths from 50 participants in the acarbose group, compared to one death (2.1%) out of 48 participants in the metformin group (RR 0.32, 95% CI 0.01 to 7.67; $P = 0.48$; 1 trial; 89 participants; very low-certainty evidence; [Analysis 2.1](#)).

Incidence of T2DM

In the acarbose group, six (13.3%) out of 45 participants developed T2DM, compared to nine (20.5%) out of 44 in the metformin group (RR 0.65, 95% CI 0.25 to 1.68; $P = 0.38$; 1 trial; 89 participants; very low-certainty evidence; [Analysis 2.2](#)).

Secondary outcomes

Measures of blood glucose control

Fasting plasma glucose

The MD in change in fasting plasma glucose for acarbose versus metformin was -0.39 mmol/L (95% CI -1.14 to 0.36; $P = 0.31$; 1 trial; 89 participants; [Analysis 2.3](#)).

2-hour plasma glucose concentrations (OGTT)

The MD in change in post-load glucose for acarbose versus metformin was -1.40 mmol/L (95% CI -2.25 to -0.55; $P = 0.001$; 1 trial; 89 participants; [Analysis 2.4](#)).

Plasma lipids

The MD of acarbose compared with metformin for total cholesterol was 0.90 mmol/L (95% CI 0.19 to 1.61; $P = 0.01$; 1 trial; 89 participants; [Analysis 2.5](#)).

The MD in change in triglycerides for acarbose versus metformin was 0.70 mmol/L (95% CI -0.06 to 1.46; $P = 0.07$; 1 trial; 89 participants; [Analysis 2.6](#)).

Body weight

The MD in change in BMI for acarbose versus metformin was -0.4 kg/m² (95% CI -1.5 to 0.7; $P = 0.48$; 1 trial; 89 participants; [Analysis 2.7](#)).

Blood pressure

The MD of acarbose compared with metformin for diastolic blood pressure was 6 mmHg (95% CI 3 to 9; $P = 0.0002$; 1 trial; 89 participants; [Analysis 2.8](#)).

For systolic blood pressure this was 1 mmHg (95% CI -5 to 7; $P = 0.32$; 1 trial; 89 participants; [Analysis 2.9](#)).

Alpha-glucosidase inhibitors versus diet or exercise, or both

One trial investigated the comparison acarbose versus diet and exercise ([Fang 2004](#)) and another trial investigated the comparison voglibose versus diet and exercise ([ABC 2017](#)).

Neither of the trials reported serious adverse events, amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, hypoglycaemia, health-related quality of life, time to progression to T2DM, or socioeconomic effects.

Primary outcomes

All-cause mortality

No participants in either the acarbose or the diet and exercise groups died in [Fang 2004](#) (very low-certainty evidence).

[ABC 2017](#) reported that 11 (2.6%) out of 424 died in the voglibose group, compared to six (1.4%) out of 435 in the diet and exercise group (RR 1.88, 95% CI 0.70 to 5.04; $P = 0.21$; 1 trial; 859 participants; very low-certainty evidence; [Analysis 3.1](#)).

Incidence of T2DM

[Fang 2004](#) reported that six (13.3%) out of 45 participants in the acarbose group developed T2DM, compared to 12 (33.3%) out of 36 in the diet and exercise group (RR 0.40, 95% CI 0.17 to 0.96; $P = 0.04$; 1 trial; 81 participants; low-certainty evidence; [Analysis 3.2](#)).

[ABC 2017](#), which compared voglibose with diet and exercise did not report T2DM incidence.

Secondary outcomes

Cardiovascular mortality

[ABC 2017](#) reported that one (0.2%) participant out of 424 in the voglibose group died of cardiovascular causes, compared to none out of 435 in the diet and exercise group (RR 3.08, 95% CI 0.13 to 75.34; $P = 0.49$; 1 trial; 859 participants; very low-certainty evidence; [Analysis 3.3](#)).

Non-fatal myocardial infarction

[ABC 2017](#) reported that 10 (2.4%) out of 424 participants in the voglibose group experienced a non-fatal myocardial infarction, compared to nine (2.1%) out of 435 in the diet and exercise group (RR 1.14, 95% CI 0.47 to 2.78; $P = 0.77$; 1 trial; 859 participants; very low-certainty evidence; [Analysis 3.4](#)).

Non-fatal stroke

[ABC 2017](#) reported that one participant (0.2%) out of 424 participants in the voglibose group experienced a non-fatal stroke, compared to three (0.7%) out of 435 in the diet and exercise group (RR 0.34, 95% CI 0.04 to 3.27; $P = 0.35$; 1 trial; 859 participants; very low-certainty evidence; [Analysis 3.5](#)).

Congestive heart failure

[ABC 2017](#) reported that four (0.9%) out of 424 participants in the voglibose group experienced congestive heart failure, compared to eight (1.8%) out of 435 in the diet and exercise group (RR 0.51, 95% CI 0.16 to 1.69; $P = 0.27$; 1 trial; 859 participants; very low-certainty evidence; [Analysis 3.6](#)).

Non-serious adverse events

[ABC 2017](#) reported that 89 (21%) out of 424 participants in the voglibose group experienced non-serious adverse events, compared to 49 (11.3%) out of 435 in the diet and exercise group (RR 1.86, 95% CI 1.35 to 2.57; $P < 0.001$; 1 trial; 859 participants; [Analysis 3.7](#)). The most common non-serious adverse events were gastrointestinal disorders, with 36 cases (8.5%) of gastrointestinal disorders in the voglibose group and 3 (0.7%) cases in the control group.

Measures of blood glucose control

Fasting plasma glucose

Acarbose reduced fasting blood glucose by -1.37 mmol/L (95% CI -0.50 to -2.24 ; $P = 0.002$; 1 trial; 81 participants; [Analysis 3.8](#); [Fang 2004](#)).

The MD in change in fasting plasma glucose for voglibose versus diet and exercise was -1.00 mmol/L (95% CI -3.44 to 1.44 ; $P = 0.42$; 1 trial; 428 participants; [Analysis 3.8](#); [ABC 2017](#)).

2-hour plasma glucose concentrations (OGTT)

Acarbose reduced post-load blood glucose by -2.79 mmol/L (95% CI -1.79 to -3.79 ; $P < 0.0001$; 1 trial; 81 participants; [Analysis 3.9](#); [Fang 2004](#)).

The MD in change in post-load blood glucose for voglibose versus diet and exercise was 0.70 mmol/L, 95% CI -7.53 to 8.93 ; $P = 0.87$; 1 trial; 391 participants; [Analysis 3.9](#); [ABC 2017](#)).

HbA1c

The MD in change in HbA1c for voglibose versus diet and exercise was 0.1% (95% CI -0.3 to 0.5 ; $P = 0.58$; 1 trial; 531 participants; [Analysis 3.10](#); [ABC 2017](#)).

Plasma lipids

The MD in change in total cholesterol for acarbose versus diet and exercise was -0.50 mmol/L (95% CI -1.33 to 0.33 ; $P = 0.24$; 1 trial; 81 participants; [Analysis 3.11](#); [Fang 2004](#)).

The MD in change in total cholesterol for voglibose versus diet and exercise was 0.00 mmol/L (95% CI -6.47 to 6.47 ; $P = 1.00$; 1 trial; 505 participants; [Analysis 3.11](#); [ABC 2017](#)).

The MD in change in triglycerides for acarbose versus diet and exercise was -0.10 mmol/L (95% CI -0.76 to 0.56 ; $P = 0.77$; 1 trial; 81 participants; [Analysis 3.12](#); [Fang 2004](#)).

The MD in change in triglycerides for voglibose versus diet and exercise was -0.10 mmol/L, 95% CI -17.03 to 16.83 ; $P = 0.99$; 1 trial; 531 participants; [Analysis 3.12](#); [ABC 2017](#)).

The MD in change in HDL-cholesterol for voglibose versus diet and exercise was 0.00 mmol/L (95% CI -2.51 to 2.51 ; $P = 1.00$; 1 trial; 545 participants; [Analysis 3.13](#); [ABC 2017](#)).

Body weight

The MD in change in BMI for acarbose versus diet and exercise was -0.2 kg/m² (95% CI -1.1 to 0.7 ; $P = 0.67$; 1 trial; 81 participants; [Analysis 3.14](#); [Fang 2004](#)).

Blood pressure

The MD in change in diastolic blood pressure for acarbose versus diet and exercise was 3 mmHg (95% CI -0.1 to 6 ; $P = 0.06$; 1 trial; 81 participants; [Analysis 3.15](#); [Fang 2004](#)).

The MD in change in diastolic blood pressure for voglibose versus diet and exercise was 0 mmHg (95% CI -2 to 2 ; $P = 1.00$; 1 trial; 586 participants; [Analysis 3.15](#); [ABC 2017](#)).

The MD in change in systolic blood pressure for acarbose versus diet and exercise was -6 mmHg (95% CI -12 to 0.2 ; $P = 0.06$; 1 trial; 81 participants; [Analysis 3.16](#); [Fang 2004](#)).

The change in systolic blood pressure for voglibose versus diet and exercise was 1.00 mmHg (95% CI -2 to 4; $P = 0.50$; 1 trial; 587 participants; [Analysis 3.16](#); [ABC 2017](#)).

Alpha-glucosidase inhibitors versus no intervention

Four trials compared acarbose with no intervention ([Fang 2004](#); [Koyasu 2010](#); [Wang 2000](#); [Yun 2016](#)).

None of the trials reported serious adverse events, amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, hypoglycaemia, health-related quality of life, time to progression to T2DM, or socioeconomic effects for this comparison.

Primary outcomes

All-cause mortality

[Fang 2004](#) and [Koyasu 2010](#) did not report any deaths in either the acarbose group or the no-intervention group ([Analysis 4.1](#); very low-certainty evidence). The other trials did not report mortality.

Incidence of T2DM

In the acarbose group, seven (9.3%) out of 75 participants developed T2DM, compared to 18 (27.7%) out of 65 in the no-intervention group (RR 0.31; 95% CI 0.14 to 0.69; $P = 0.004$; 2 trials; 140 participants; very low-certainty evidence; [Analysis 4.2](#)). Both [Fang 2004](#) and [Wang 2000](#), defined T2DM as a FPG of at least 7.8 mmol/L and a 2hPG at least 11.1 mmol/L ([WHO 1985](#)).

Secondary outcomes

Cardiovascular mortality

In the acarbose group, three (2.9%) out of 102 participants died of cardiovascular causes compared to five (4.9%) out of 103 participants in the no-intervention group (RR 0.64, 95% CI 0.16 to 2.56; $P = 0.53$; 2 trials; 205 participants; very low-certainty evidence; [Analysis 4.3](#)). There were no cases of cardiovascular mortality in [Koyasu 2010](#), so [Yun 2016](#), which included participants with acute coronary syndrome, weighs 100% in this analysis. Neither [Koyasu 2010](#) nor [Yun 2016](#) specifically defined the outcome cardiovascular mortality.

Non-fatal myocardial infarction

In the acarbose group, two (2%) out of 102 participants experienced a non-fatal myocardial infarction, compared to seven (6.8%) out of 103 in the no-intervention group (RR 0.30, 95% CI 0.07 to 1.41; $P = 0.13$; 2 trials; 205 participants; very low-certainty evidence; [Analysis 4.4](#)). There were no cases of non-fatal myocardial infarction in [Koyasu 2010](#), so again, [Yun 2016](#), which included participants with acute coronary syndrome, weighs 100% in this analysis. In both trials, the population had a history of myocardial infarction. In [Koyasu 2010](#), 42.9% of the acarbose group and 51.3% of the control group had a previous myocardial infarction. In [Yun 2016](#), this was 68.7% in the acarbose group and 63.2% in the control group.

Non-fatal stroke

In the acarbose group two (2%) out of 102 participants experienced a non-fatal stroke, compared to four (3.9%) out of 103 in the no-intervention group (RR 0.53, 95% CI 0.10 to 2.81; $P = 0.46$; 2 trials; 205 participants; very low-certainty evidence; [Analysis 4.5](#)). In [Koyasu 2010](#), there were no cases of non-fatal stroke, so here too [Yun 2016](#), which included participants with acute coronary

syndrome, weighs 100% in this analysis. Neither [Yun 2016](#) nor [Koyasu 2010](#) specifically defined non-fatal stroke.

Congestive heart failure

In the acarbose group, five (4.9%) out of 102 participants had congestive heart failure, compared to six (5.8%) out of 103 in the no-intervention group (RR 0.87, 95% CI 0.27 to 2.37; $P = 0.81$; 2 trials; 205 participants; [Analysis 4.6](#); very low-certainty evidence). [Yun 2016](#), which included participants with acute coronary syndrome, specified non-fatal heart failure as, "severe heart-failure". [Koyasu 2010](#) did not further specify the outcome.

Non-serious adverse events

One trial reported data on non-serious adverse effects ([Wang 2000](#)). Two participants in the acarbose group (6.7%) and no participants in the no-intervention group reported adverse effects (RR 5.00, 95% CI 0.25 to 99.95; $P = 0.29$; 1 trial; 60 participants; [Analysis 4.7](#)).

Hypoglycaemia

[Yun 2016](#) reported that there were no cases of hypoglycaemia in the acarbose group or the no-intervention group ([Analysis 4.8](#)).

Measures of blood glucose control

Fasting plasma glucose

The MD in change in fasting plasma glucose for acarbose versus no intervention was -0.35 mmol/L (95% CI -0.79 to 0.08; $P = 0.11$; 3 trials; 285 participants; [Analysis 4.9](#)). The 95% prediction interval ranged between -5.24 mmol/L and 4.54 mmol/L. Using the fixed-effect model the difference was -0.22 mmol/L (95% CI -0.39 to -0.06), in favour of AGI.

2-hour plasma glucose concentrations (OGTT)

The change in post-load glucose for acarbose versus no intervention ranged between -0.91 mmol/L and -4.53 mmol/L (3 trials; 285 participants; [Analysis 4.10](#)). The 95% prediction interval ranged between -23.56 mmol/L and 18.56 mmol/L.

HbA1c

The change in HbA1c for acarbose versus no intervention ranged between -0.04% and -0.5% (2 trials; 205 participants; [Analysis 4.11](#)).

Plasma lipids

The MD in change in total cholesterol for acarbose versus no intervention was -0.32 mmol/L (95% CI -0.74 to 0.10; $P = 0.13$; 3 trials; 285 participants; [Analysis 4.12](#)). The 95% prediction interval ranged between -4.83 mmol/L and 4.19 mmol/L.

For HDL-cholesterol the MD was -0.01 mmol/L (95% CI -0.10 to 0.07; $P = 0.75$; 1 trial; 81 participants; [Analysis 4.13](#); [Koyasu 2010](#)).

The MD in change in LDL-cholesterol for acarbose versus no intervention was -0.03 mmol/L (95% CI -0.22 to 0.15; $P = 0.71$; 2 trials; 205 participants; [Analysis 4.14](#)).

For triglycerides the MD was -0.22 mmol/L (95% CI -0.40 to -0.05; $P = 0.01$; 3 trials; 285 participants; [Analysis 4.15](#)). The 95% prediction interval ranged between -1.32 mmol/L and 0.88 mmol/L.

Body weight

The MD in change in body weight for acarbose versus no intervention was -1.4 kg (95% CI -2.4 to -0.4 ; $P = 0.005$; 1 trial; 81 participants; [Analysis 4.16](#)), in favour of acarbose ([Koyasu 2010](#)).

The MD in change in BMI for acarbose versus no intervention was -0.7 kg/m² (95% CI -1.0 to -0.3 ; $P = 0.0003$; 3 trials; 285 participants; [Analysis 4.17](#)). The 95% prediction interval ranged between -2.9 kg/m² and 1.6 kg/m².

Blood pressure

The MD in change in diastolic blood pressure for acarbose versus no intervention was -0.3 mmHg (95% CI -4 to 3 ; $P = 0.88$; 3 trials; 285 participants; [Analysis 4.18](#)). The 95% prediction interval ranged between -40 mmHg and 40 mmHg.

For the systolic blood pressure the MD was -4 mmHg (95% CI -7 to -1 ; $P = 0.009$; 3 trials; 285 participants; [Analysis 4.19](#)). The 95% prediction interval ranged between -22 mmHg and 14 mmHg.

DISCUSSION

Summary of main results

In the first version of this review (New Reference), we found evidence that acarbose reduces the incidence of T2DM in people with IGT, and we also concluded that acarbose may prevent the occurrence of cardiovascular events. In this update the evidence for a reduction in incidence of T2DM is confirmed. However, whether AGI prevent the underlying cause remains unclear. Furthermore, the addition of new trials to our review has made a beneficial effect of AGI on cardiovascular mortality or cardiovascular events less likely.

Overall completeness and applicability of evidence

This review includes 10 completed trials investigating the effect of AGI on the incidence of T2DM, cardiovascular events and other outcomes for one year or longer. Most trials used acarbose as the intervention, but two trials investigated voglibose ([ABC 2017](#); [Kawamori 2009](#)). All trials included both men and women and the participants were generally above 50 years old. The majority of trials were performed in China or Japan, but three trials were performed in Western countries ([DAISI 2008](#); [EDIT 1997](#); [STOP-NIDDM 2002](#)). The results may therefore be generalised to adults from both genders and from different ethnicities.

The majority of trials reported incidence of T2DM ([ACE 2017](#); [DAISI 2008](#); [Fang 2004](#); [Kawamori 2009](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#)), and all-cause mortality ([ABC 2017](#); [ACE 2017](#); [DAISI 2008](#); [Fang 2004](#); [Kawamori 2009](#); [STOP-NIDDM 2002](#); [Wang 2000](#)), whereas none of the trials reported on the secondary outcomes amputation of lower extremity, blindness or severe vision loss, end-stage renal disease, health-related quality of life, time to progression to T2DM and socioeconomic effects.

Decrease in incidence of type 2 diabetes mellitus

We found evidence from several trials that AGI reduce the incidence of T2DM ([ACE 2017](#); [Kawamori 2009](#); [Fang 2004](#); [STOP-NIDDM 2002](#); [Wang 2000](#)). An effect on the incidence of T2DM is not surprising. After all, AGI have a clear effect on glycaemic control in people with T2DM ([Van de Laar 2005](#)). Such a drug will have large effects on the 'incidence' of diabetes for people who are at the border of fulfilling

the criteria for T2DM. So, the question is whether AGI prevent, delay, or mask T2DM. The authors of [STOP-NIDDM 2002](#) are undecided, as they sometimes speak of "prevention" (in the title) and sometimes of "delay" (in the summary), ([Chiasson 2002](#) under [STOP-NIDDM 2002](#)). Critics of [STOP-NIDDM 2002](#) suggested that acarbose masks T2DM, since 15.4% of the participants on acarbose compared to 10.6% on placebo converted to T2DM during a three-month wash-out phase ([Kaiser 2004](#)). The authors of [ACE 2017](#) speak of a reduced risk of T2DM, but do not go into detail about whether this reflects prevention, delay or masking of T2DM.

To assess the value of AGI with respect to the effects on the development of T2DM, it is probably more straightforward to look at the effects on glycaemic control. After all, IGT refers to an intermediate state between normal glucose homeostasis and T2DM. In our meta-analysis we found a reduction in HbA1c (-0.08% , 95% CI -0.12 to -0.05), fasting blood glucose (-0.07 mmol/L, 95% CI -0.12 to -0.02), and 2-hour plasma glucose (-0.53 mmol/L, 95% CI -0.92 to -0.14), when comparing acarbose to placebo. When comparing acarbose to no intervention, only the 2-hour plasma glucose showed a decrease (-2.50 mmol/L, 95% CI -4.18 to -0.83). Those effects are mostly smaller than obtained in a Cochrane Review on alpha-glucosidase inhibitors for people with T2DM ([Van de Laar 2005](#)). This may be explained by the fact that the before-mentioned review found that the effects on glycaemic control were less strong with lower baseline values of glycaemia and longer trial duration. A decrease of 0.07 mmol/L for fasting plasma glucose and a decrease of 0.53 mmol/L for post-load glucose does not seem to fully explain the decrease in T2DM diabetes incidence we found. This would suggest that AGI do in fact target the underlying pathophysiology.

Most trials in the Cochrane Review studied post-load glucose with an oral glucose tolerance test (OGTT) ([ABC 2017](#); [DAISI 2008](#); [Kawamori 2009](#); [Koyasu 2010](#); [STOP-NIDDM 2002](#); [Yun 2016](#)). Acarbose has no direct effects on an OGTT as alpha-glucosidase inhibitors only delay the breakdown of complex polysaccharides (and not monosaccharides such as glucose). In this light the decreasing effect of acarbose on a 2-hour OGTT is positive because it indicates a beneficial effect on insulin resistance.

Another argument in the question whether an effect of AGI on the incidence of T2DM is relevant or important, is the desirability of a drug intervention in people at high risk for T2DM. It is well recognised that the increase in the number of people with T2DM is due to 'lifestyle' factors such as a shortage of exercise and an unhealthy diet. Focusing on drugs as the solution of the problem may distract people from the issues that are truly important: eat less and exercise more ([Hemmingsen 2017a](#); [Hopper 2011](#)).

Finally the question arises whether true (primary), prevention of T2DM with a single drug is possible at all. T2DM is a complex disease in which many pathophysiological mechanisms are involved (for example insulin sensitivity and blood pressure regulation). Only when one predominant mechanism was identified, would primary prevention by a drug targeting this mechanism be feasible. Currently, it seems unlikely that this will be the case for T2DM in the near future. In the meanwhile, drug interventions for IGT should be regarded as secondary or tertiary prevention.

Decrease in incidence of cardiovascular disease

The observed beneficial effects on the occurrence of cardiovascular morbidity ([STOP-NIDDM 2002](#)) are interesting. However, these results should be interpreted with great prudence. This is

underlined by the study authors, who sensibly stated that because effects on cardiovascular morbidity were secondary objectives and the number of events was relatively small, they should be seen as hypothesis-generating (Chiasson 2004 under [STOP-NIDDM 2002](#)).

Critics mentioned the skewed discontinuation rate as another explanation for the observed effects, rather than an effect of acarbose ([Sawicki 2004](#)). Because more participants in the acarbose group stopped taking their medication (mostly due to adverse effects), the participants in the acarbose group were not followed up as regularly as the participants in the placebo group and could have had therefore less chance to be 'detected' in case a cardiovascular event had taken place. We reanalysed the data accounting for differences in follow-up rate and found that the odds ratios for the occurrence of any cardiovascular event became less strong, but remained statistically significant.

Another explanation could be in the existence of (unknown) confounding factors. The cost-effectiveness subtrial of [STOP-NIDDM 2002](#) ([Quilici 2005](#)), reported clues for differences in treatment groups. They determined baseline risk profiles with a formula for the identification of high risk for T2DM ([Stern 2002](#)), or cardiovascular risk ([Anderson 1991](#)). Based on these risk scores, they stated that "... more placebo patients than acarbose-treated patients were represented in the high-risk subgroups...". Therefore, participants in the placebo group could have had a higher a-priori risk than participants in the acarbose group.

The other trials that looked at cardiovascular mortality and morbidity found no beneficial effect of AGI. The trials looking at acarbose used a lower dose than [STOP-NIDDM 2002](#) (50 mg three times daily and 100 mg three times daily, respectively), which might indicate a dose-response relationship. The authors of [ACE 2017](#) also mentioned that their population was on average younger than the [STOP-NIDDM 2002](#) population and that there was a difference in ethnicity. [ACE 2017](#), which included participants with coronary heart disease, recommended more aggressive, secondary cardiovascular prevention measures, which might explain the difference in effect found in [ACE 2017](#) compared to [STOP-NIDDM 2002](#), which excluded participants with a recent cardiovascular event.

[ABC 2017](#) included participants with clinically overt myocardial infarction, and found no beneficial effect for voglibose in reducing cardiovascular mortality and morbidity. In fact, the HR leaned towards no intervention being more beneficial. Interestingly, the voglibose group had a considerably larger portion of people using anti-platelet therapy at baseline than the control group (417 (96.5%) and 382 (92.5%) respectively). This could mean the voglibose group was better protected against cardiovascular events than the control group. On the other hand, it might also mean that the control group had more morbidity at baseline and thus a higher risk.

Several trials included participants with a history of cardiovascular disease ([ABC 2017](#); [ACE 2017](#); [Yun 2016](#); [Koyasu 2010](#)). These participants were therefore at a higher baseline risk for cardiovascular events compared to the trials that included participants with no such history. We still believe these trials to be comparable, because, despite baseline differences, the effect of AGI on cardiovascular events should be the same.

As none of the trials included in this review, besides [STOP-NIDDM 2002](#), showed any benefit of AGI in the prevention of either cardiovascular mortality or morbidity, we conclude that there is no proof that AGI are effective in preventing cardiovascular disease, cardiovascular mortality or both.

Effects on incidence of hypertension

In one trial the authors reported a beneficial effect on the incidence of new cases of hypertension ([STOP-NIDDM 2002](#)). It is remarkable that at baseline almost half of all participants were already diagnosed with hypertension (acarbose 357/682, placebo 345/686), but these participants were kept in the analysis for the development of hypertension.

We could not confirm the beneficial effects on hypertension observed in [STOP-NIDDM 2002](#), in which hypertension was studied as a clinical outcome (blood pressure greater than 140/90 mmHg on two or more occasions). Instead we studied the differences in diastolic and systolic blood pressure. These outcomes yielded an effect of acarbose compared to no intervention on systolic blood pressure (-4 mmHg, 95% CI -7 to -1) ([Fang 2004](#); [Koyasu 2010](#); [Yun 2016](#)), no clear effects of AGI compared to placebo ([ACE 2017](#); [STOP-NIDDM 2002](#)), and a detrimental effect of acarbose compared to metformin in one trial (6 mmHg, 95% CI 3 to 9) ([Fang 2004](#)).

Strengths and limitations of the review

One of the main strengths of this review is the rigorousness and completeness of the search. Second, the a priori decision to only include randomised trials with a duration of at least one year ensured a 'minimum level' of quality. Third, we assessed many different outcomes in the review, which enables the readers to judge by themselves what matters most for their own particular question. Finally, we think that the tables and figures and the extensive provision of all outcome data and information related to quality and heterogeneity, make the review transparent.

One of the limitations is the missing data from [EDIT 1997](#). Regrettably, the trial authors are not willing to share their data before their trial is published. They have kindly promised their help once their manuscripts are accepted for publication, but the analysis of the data still needs to be completed. It is regrettable that this important trial has not been published yet (August 2018). This points to a possible time lag bias: a kind of reporting bias in which trials may be published rapidly or delayed depending on the nature and direction of the results. Of course we will use upcoming data from this trial. Another limitation is the external validity of the results. For some trials, the recruitment of the participants was not clearly described ([EDIT 1997](#); [Fang 2004](#); [Wang 2000](#)). It is important to know how selection took place in order to be able to generalise the results to other clinical settings. For example, were the participants volunteers recruited with a newspaper advertisement (and thus highly motivated), or were they recruited from the files of general practitioners (and maybe less motivated)? Further, we only found two trials with voglibose as the AGI. Whether the results may be extrapolated to miglitol depends on the existence of a possible group effect for AGI. The data from the voglibose trials seem in line with the acarbose data, but more trials would be needed to determine whether a group effect exists. The Cochrane Review on AGI for T2DM, obtained comparable results for acarbose and miglitol for most outcomes ([Van de Laar 2005](#)). Another limitation is that the included trials focused on participants with IGT, which means the results of the meta-

analysis cannot simply be applied to people with IFG or elevated HbA1c. A further limitation is that in the comparison of acarbose and placebo, there were outcomes where [ACE 2017](#) contributed most weight. These outcomes were incidence of T2DM, serious adverse events, cardiovascular mortality and congestive heart failure. Moreover, we did not perform the subgroup and sensitivity analyses that we had planned to do. This was due to the relatively large heterogeneity between the included trials. There were not enough trials with the same intervention and control group to further divide these into subgroups. Lastly, there was considerable heterogeneity in some of the meta-analyses (2hPG, body weight, and BMI in the acarbose versus placebo group comparison, and FPG, 2hPG, HbA1c, and diastolic blood pressure in the acarbose versus no intervention comparison). The heterogeneity for FPG and 2hPG in the acarbose versus no-intervention group comparison might be explained by an inadequate randomisation in [Fang 2004](#), which meant that the acarbose group had a considerably higher baseline 2hPG than the no-intervention group. It is unclear what exactly caused the heterogeneity in the other analyses.

A point of concern could be that due to changing cut-off thresholds, the diagnostic criteria for intermediate hyperglycaemia varied among trials. In 1985, the WHO criteria for IGT were a fasting plasma glucose of more than 7.8 mmol/L and a 2hPG of 7.8 to 11.1 mmol/L ([WHO 1985](#)). In 1998, the FPG limit was lowered to 7.0 mmol/L ([WHO 1998](#)). The cut-off levels for post-load glucose were quite similar among trials (7.8 to 11.1 mmol/L for 2hPG), with the exception of [DAISI 2008](#), where the trialists used 8.6 mmol/L as the lower limit. But with respect to FPG, the older trials used 7.7 mmol/L or 7.8 mmol/L as the upper limit ([DAISI 2008](#); [EDIT 1997](#); [Fang 2004](#); [STOP-NIDDM 2002](#); [Wang 2000](#)), and the more recent trials used either 6.9 mmol/L or 7.0 mmol/L as the upper limit ([ABC 2017](#); [ACE 2017](#); [Kawamori 2009](#); [Koyasu 2010](#)). The one exception is [Yun 2016](#), which used a FPG of 6.1 mmol/L as the upper limit. Consequently, it is likely that some older trials will have included participants that nowadays would be categorised as having T2DM. We think that this will have a negligible effect on generalisability because there is no clear border between 'prediabetes' and diabetes, and the number of participants involved is limited. Namely, the average baseline FPG value in [DAISI 2008](#) was 6.5 mmol/L for the control group and 6.6 mmol/L for the intervention group; in [Fang 2004](#) the baseline FPG value was 6.5 mmol/L in the acarbose group, 5.7 mmol/L in the no-intervention group, 6.3 mmol/L in the metformin group and 5.6 mmol/L in the diet and exercise group; in [EDIT 1997](#) the baseline FPG value was 6.0 mmol/L in both groups; and for [STOP-NIDDM 2002](#) it was 6.2 mmol/L in both groups, which means the average baseline FPG values are below the current cut-off value of 7.0 mmol/L for the diagnosis of T2DM. The baseline FPG values for one trial were not available ([Wang 2000](#)).

It is also worth mentioning that we were unable to find the information in trials registers for a surprising number of trials ([Fang 2004](#); [Yun 2016](#)). Consequently, we were not able to determine if any changes to the protocol had been made during these trials.

Quality of the evidence

For the comparison of acarbose with placebo the main reason for downgrading the certainty of the evidence of outcomes detailed in the [Summary of findings for the main comparison](#) was imprecision, usually because of the small number of trials, CIs consistent with benefit and harm or both. This also holds true for the comparison of voglibose with placebo.

For the single small trial evaluating acarbose with metformin, the single small trial on acarbose as well the single larger trial on voglibose, all compared to diet, exercise or both, we downgraded the certainty of the evidence for all reported outcomes, mainly due to imprecision.

Lastly, for the comparison of acarbose with no intervention, we downgraded the certainty of the evidence of outcomes detailed in [Summary of findings 2](#), again mainly due to imprecision, because of the small number of participants and events, and the small number of trials.

Most evidence was of either low or very low quality and should be interpreted accordingly.

Potential biases in the review process

In updating this review, we adhered to the original protocol. A point of potential bias could be that four trials included participants who had established cardiovascular morbidity at the time of randomisation ([ABC 2017](#); [ACE 2017](#); [Koyasu 2010](#); [Yun 2016](#)). In clinical practice, 'prediabetes' is often diagnosed following a cardiovascular event. As such, these participants are the target group for this intervention and are therefore included in this review alongside the participants without cardiovascular morbidity. We planned to perform a subgroup analysis with the trials that included participants with established cardiovascular morbidity, but due to the low number of trials and the variability in control groups between these trials, this was not possible.

Agreements and disagreements with other studies or reviews

A systematic review that looked at the effectiveness of behaviour-changing, pharmacological and surgical interventions in preventing T2DM also found that AGI were effective in preventing T2DM, but other interventions were more effective (namely glipizide and diet combined with pioglitazone) ([Stevens 2015](#)). Another systematic review studied the effects of behaviour-changing and pharmacological interventions in preventing cardiovascular events in people with 'prediabetes'. It found that both pharmacological and behaviour-changing interventions were beneficial in preventing T2DM (RR 0.66, 95% CI 0.55 to 0.80), though behaviour-changing interventions were more effective than pharmacological interventions (RR 0.52, 95% CI 0.46 to 0.58 versus RR 0.70, 0.58 to 0.85 respectively). However, neither was beneficial in reducing cardiovascular mortality, all-cause mortality and myocardial infarction. The only outcome pharmacological interventions might prevent according to this review were fatal and non-fatal strokes (RR 0.76, CI 0.58 to 0.99; [Hopper 2011](#)).

A recent Cochrane Review on the effects of diet, physical activity or both in people at increased risk of T2DM found that a combination of diet and physical activity reduced the incidence of T2DM compared to standard or no treatment (RR 0.57, 95% CI 0.50 to 0.64; [Hemmingsen 2017a](#)).

AUTHORS' CONCLUSIONS

Implications for practice

In people with intermediate hyperglycaemia the use of alpha-glucosidase inhibitors reduces or delays the incidence of type 2 diabetes mellitus, but it is unclear whether it actually prevents

the underlying cause. Most of the evidence originated from a trial that included participants with coronary heart disease and impaired glucose tolerance. There is no firm evidence that alpha-glucosidase inhibitors prevent cardiovascular mortality and morbidity. If physicians and people with increased risk of type 2 diabetes mellitus feel that an active treatment for intermediate hyperglycaemia is needed, they should carefully consider this evidence together with evidence for other interventions, especially behaviour-changing interventions.

Implications for research

The disclosure of the finished – but still unpublished – [EDIT 1997](#) trial would be useful for a potential future update of this review. Due to the heterogeneity of the included trials, more trials would likely not help us to come to a firm conclusion. If planned, new long-term

and adequately powered trials should focus on patient-important outcomes such as health-related quality of life and micro- and macrovascular complications associated with diabetes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ABC 2017

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: individuals with clinically overt MI, 21-79 years old with IGT (fasting plasma glucose levels of ≤ 7.0 mmol/L, a 2-h OGTT value of between 7.8-11.1 mmol/L, and HbA1c levels of $\leq 6.5\%$)</p> <p>Exclusion criteria: acute MI occurring within the last 7 d; patients with NYHA symptoms of $\geq$ class II or with a LVEF of $\leq 40\%$; suspected type I DM; patients scheduled for coronary angioplasty; history of coronary artery bypass graft surgery; serious liver or kidney damage; history of allergy or drug hypersensitivity; arteriosclerosis obliterans with Fontaine stage III or worse; and inability to understand and/or comply with trial medications, procedures, and/or follow-up or any conditions that may render the participant unable to complete the trial in the opinion of the investigator</p>

ABC 2017 (Continued)

Diagnostic criteria:

FPG $\leq$ 7.0 mmol/L and 2hPG of 7.8-11.1 mmol/L ([WHO/IDF 2006](#))

HbA1c $\leq$ 6.5%

Interventions	<p>Number of trial centres: 112</p> <p>Run-in period: no</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 0.2 mg voglibose 3 times/d (in the event of gastrointestinal side effects the dosage was reduced to half or a quarter of the original dosage)</p> <p>Control: diet and exercise therapy</p>
Outcomes	<p>Composite outcome measures reported: yes, the time until the first cardiovascular composite end-point of death from cardiovascular death, hospitalisation due to non-fatal MI, non-fatal unstable angina, non-fatal stroke, or treatment with coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft)</p>
Study details	<p>Trial terminated early (because of lack of benefit): yes</p> <p>Trial ID: NCT00212017</p>
Publication details	<p>Language of publication: English</p> <p>Funding: non-commercial funding</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	<p>Quote from publication: "... to evaluate effects of aggressive intervention with the alpha-glucose inhibitor voglibose on cardiovascular events in patients with IGT and a history of MI"</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All patients were randomly assigned (1:1) through a web-based central randomisation system using computer-generated random numbers (NTT Data, Tokyo, Japan)"
Allocation concealment (selection bias)	Low risk	Quote: "This study was open-labeled, and allocation was unmasked to the patients and investigators, but masked to the event adjudication committee and the data and safety monitoring board (DSMB)"
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Comment: open-label, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias)	Low risk	Comment: open-label, but we judged the outcome unlikely to be influenced by lack of blinding

ABC 2017 (Continued)

measures of blood glucose control

Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: open-label, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-serious adverse events	High risk	Comment: open-label
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Quote: "...allocation was [...] masked to the event adjudication committee and the data and safety monitoring board (DSMB)"
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote: "...allocation was [...] masked to the event adjudication committee and the data and safety monitoring board (DSMB)"
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "...allocation was [...] masked to the event adjudication committee and the data and safety monitoring board (DSMB)"
Blinding of outcome assessment (detection bias) non-serious adverse events	Low risk	Quote: "...allocation was [...] masked to the event adjudication committee and the data and safety monitoring board (DSMB)"
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	Low risk	Comment: 424 completers and 4 dropouts in treatment group, 435 completers and 4 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Comment: 424 completers and 4 dropouts in treatment group, 435 completers and 4 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: 424 completers and 4 dropouts in treatment group, 435 completers and 4 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-serious adverse events	Low risk	Comment: 424 completers and 4 dropouts in treatment group, 435 completers and 4 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%

ABC 2017 (Continued)

Selective reporting (reporting bias)	High risk	Comment: the secondary outcomes mentioned in the trial register were slightly different in the publication (all-cause mortality; hospitalisation due to heart failure, CAD, and cerebrovascular disease; progression of IGT to diabetes; development or deterioration of hypertension or hyperlipidaemia; and deterioration of renal function), compared to: all-cause mortality; hospitalisation due to heart failure; death from cardiovascular disease, non-fatal myocardial infarction, non-fatal unstable angina, treatment with coronary revascularisation, non-fatal stroke)
Other bias	High risk	Comment: the trial was terminated early and the main researchers received grants and personal fees from Pfizer and Takeda.

ACE 2017

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Male or female, aged ≥ 50 years Definite coronary heart disease, defined below: Previous MI or ACS, but not within the last 3 months, with any 2 of the following: <ul style="list-style-type: none"> * typical clinical presentation * confirmatory ECG changes * appropriate elevation of cardiac enzymes/biomarkers Previous UA or ACS, but not within the last 3 months, with any 2 of the following: <ul style="list-style-type: none"> * typical clinical presentation * confirmatory ECG changes * either elevation of a cardiac biomarker or a $> 50\%$ stenosis in ≥ 1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories 'moderate' and 'severe' will be taken as equating to $> 50\%$ stenosis. Current stable angina defined as: <ul style="list-style-type: none"> * typical clinical history with symptoms occurring within the last month, and * a $> 50\%$ stenosis in ≥ 1 major epicardial coronary artery shown on coronary angiography or CT angiography. Where stenosis is reported in a qualitative manner, the categories 'moderate' and 'severe' will be taken as equating to $> 50\%$ stenosis. IGT diagnosed on a single standard OGTT, defined as a 2hPG value ≥ 7.8 but < 11.1 mol/L and a fasting plasma glucose (FPG) < 7.0 mmol/L within 6 months prior to enrolment Optimised cardiovascular drug therapy At least 80% adherent to single-blind placebo study medication during the run-in period Provision of written informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Previous history of diabetes, other than gestational diabetes MI, UA, stroke or TIA within the previous 3 months Planned or anticipated coronary, cerebrovascular or peripheral arterial revascularisation or other major surgical intervention, at the time of randomisation NYHA class III or IV heart failure Evidence of severe hepatic disease Evidence of severe renal impairment or an eGFR < 30 mL/min/1.73m² (derived using the Chinese MDRD equation) Any other condition likely to reduce adherence to the protocol e.g. alcoholism, major active psychiatric disorder, cognitive impairment or a condition likely to markedly limit life expectancy e.g. malignancy

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- Pregnancy (or planned pregnancy within the next 5 years)
- Concurrent participation in any other clinical interventional trial. Note: participants who were treated previously with an alpha-glucosidase inhibitor must have at least a 3-month washout period before being randomised into the ACE trial
- Known intolerance to AGI or gastrointestinal problems
- Thought by the investigator for any reason to be unsuitable for participation in this clinical study

Diagnostic criteria:

FPG < 7.0 mmol/L and 2hPG of 7.8-11.1 mmol/L ([WHO/IDF 2006](#))

Interventions	<p>Number of study centres: 176</p> <p>Run-in period: 4 weeks with placebo medication, optimisation of cardiovascular therapy, and provision of lifestyle advice with respect to diet, exercise, and smoking</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 50 mg acarbose 3 times/d with meals</p> <p>Control: placebo 3 times/d with meals</p>
Outcomes	<p>Composite outcome measures reported: yes, a 5-point composite of cardiovascular death, non-fatal MI, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure</p>
Study details	<p>Trial terminated early: no</p> <p>Trial ID: NCT00829660</p>
Publication details	<p>Language of publication: English</p> <p>Funding: commercial funding (Bayer)</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	<p>Quote from publication: "The Acarbose Cardiovascular Evaluation (ACE) trial was designed to examine whether acarbose could reduce cardiovascular events in Chinese patients with established coronary heart disease and IGT, and whether the incidence of type 2 diabetes could be reduced"</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned (1:1) by a centralised computer system to receive either acarbose or to matching placebo, in blocks of eight within site. The randomisation sequence (coded as A or B) was generated by a Diabetes Trials Unit statistician unconnected to the trial and uploaded to the electronic Rave Trial Management System (rTMS)"
Allocation concealment (selection bias)	Low risk	Quote: "Acarbose and matching placebo tablets were provided by Bayer AG, packaged in 4-month quantities, each packet being labelled with a unique code. These codes were also uploaded to the rTMS with their corresponding A or B categorisation, which was not visible to study staff"
Blinding of participants and personnel (performance bias)	Low risk	Comment: double-blind, using a matched placebo

ACE 2017 (Continued)

all-cause/cardiovascular
mortality

Blinding of participants and personnel (performance bias) hypoglycaemia	Low risk	Comment: double-blind, using a matched placebo
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: double-blind, using a matched placebo
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: double-blind, using a matched placebo
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: double-blind, using a matched placebo
Blinding of participants and personnel (performance bias) non-serious adverse events	Low risk	Comment: double-blind, using a matched placebo
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	Comment: double-blind, using a matched placebo
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Quote: "Potential cardiovascular endpoint events were reviewed and adjudicated by an independent cardiovascular endpoint adjudication committee, which was masked to treatment allocation"
Blinding of outcome assessment (detection bias) hypoglycaemia	Low risk	Quote: "...at subsequent study visits, investigators were instructed by the rTMS which study medication packet should be given to each participant. They were required to enter two letters printed alongside the unique code on the packet label so that the rTMS could confirm the correct study medication had been dispensed. Up until database lock, the assignment of A or B to active or placebo was known only to the Bayer AG study medication packaging group and the data and safety monitoring board"
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Quote: "An independent diabetes endpoint adjudication committee masked to treatment group allocation reviewed cases in which diabetes was diagnosed, or in which participants were commenced on other glucose-lowering drugs, outside of the trial to decide if a diagnosis of diabetes was warranted"
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote: "...at subsequent study visits, investigators were instructed by the rTMS which study medication packet should be given to each participant. They were required to enter two letters printed alongside the unique code on the packet label so that the rTMS could confirm the correct study medication had been

ACE 2017 (Continued)

		dispensed. Up until database lock, the assignment of A or B to active or placebo was known only to the Bayer AG study medication packaging group and the data and safety monitoring board"
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "Potential cardiovascular endpoint events were reviewed and adjudicated by an independent cardiovascular endpoint adjudication committee, which was masked to treatment allocation"
Blinding of outcome assessment (detection bias) non-serious adverse events	Low risk	Quote: "...at subsequent study visits, investigators were instructed by the rTMS which study medication packet should be given to each participant. They were required to enter two letters printed alongside the unique code on the packet label so that the rTMS could confirm the correct study medication had been dispensed. Up until database lock, the assignment of A or B to active or placebo was known only to the Bayer AG study medication packaging group and the data and safety monitoring board"
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	Quote: "...at subsequent study visits, investigators were instructed by the rTMS which study medication packet should be given to each participant. They were required to enter two letters printed alongside the unique code on the packet label so that the rTMS could confirm the correct study medication had been dispensed. Up until database lock, the assignment of A or B to active or placebo was known only to the Bayer AG study medication packaging group and the data and safety monitoring board"
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) hypoglycaemia	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-serious adverse events	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) serious adverse events	Low risk	3092 completers and 180 dropouts in treatment group, 3064 completers and 186 dropouts in control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%

ACE 2017 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: no changes between design paper and final publication, except for the original primary composite cardiovascular outcome, a 3-point MACE outcome, which was changed to a 5-point major cardiovascular event, but this change was explained in the final publication
Other bias	High risk	Comment: the main researcher received grants from Bayer

DAISI 2008

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: IGT (a mean fasting plasma glucose level > 5.5 mmol/L and < 7.8 mmol/L, a mean 2-h PG level of 8.6-11.1 mmol/L, an HbA1c level ≤ 7.0% and aged 45-70 years) At the end of the qualification period, participants were considered eligible if they met the following criteria: having complied with the study procedures, having taken more than 80% of the prescribed medication during week 3-6 of the qualification period (as determined from returned tablet blisters), and having reported no adverse effects that could threaten future compliance</p> <p>Exclusion criteria: diseases or conditions likely to prevent completion of the study, known uncorrected endocrine disorders, documented gastrointestinal diseases, cholesterol > 10 mmol/L or triglycerides > 10 mmol/L, treatment with lipid-lowering medication (with the exception of statins), MI within the previous 6 months, impaired liver function (AST/ALT > 50 units/L), or impaired kidney function (creatinine > 150 mmol/L)</p> <p>Diagnostic criteria:</p> <p>FPG < 7.8 mmol/L (WHO 1985) 2hPG: 8.6 to 11.1 mmol/L</p>
Interventions	<p>Number of study centres: single centre</p> <p>Run-in period: a qualification period over 6 weeks with acarbose treatment for all participants, and a wash-out period over 4 weeks with placebo treatment for all participants</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 50 mg acarbose 3 times/d</p> <p>Control: placebo 3 times/d</p>
Outcomes	Composite outcome measures reported: no
Study details	<p>Trial terminated early: no</p> <p>Trial ID: NTR150</p>
Publication details	<p>Language of publication: English</p> <p>Funding: commercial funding (Bayer)</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	Quote from publication: "To investigate the effects of acarbose on the distribution of the 2-h plasma glucose level following an intake of 75 g of glucose, the incidence of conversion to type 2 dm, on insulin secretion induced by hyperglycemia and on insulin sensitivity"

DAISI 2008 (Continued)

Notes

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Study numbers were randomly assigned to the placebo or the acarbose group generated by a computer at Bayer's biometric unit. The numbers were assigned in ascending order in the sequence of the subject's entry into the intervention study."
Allocation concealment (selection bias)	Low risk	Quote: "Study numbers were randomly assigned to the placebo or the acarbose group generated by a computer at Bayer's biometric unit. The numbers were assigned in ascending order in the sequence of the subject's entry into the intervention study."
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of participants and personnel (performance bias) non-serious adverse events	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	Quote: "Double-blind. [...] Placebo tablets matched the acarbose tablets in size, shape, and colour"
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"

DAISI 2008 (Continued)
incidence of T2DM

Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"
Blinding of outcome assessment (detection bias) non-serious adverse events	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	Quote: "The identity of the treatment groups was concealed until the final statistical analysis"
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) non-serious adverse events	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) serious adverse events	High risk	Comment: 30 completers and 30 dropouts in treatment group, 36 completers and 22 dropouts in control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Selective reporting (reporting bias)	Low risk	Comment: outcomes in trial register and publications are the same
Other bias	Unclear risk	Comment: possible funding bias

EDIT 1997

Methods	Factorial RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: 30-70 years, "at risk for developing diabetes", 2 consecutive FPG levels of 5.5-7.7 mmol/L</p> <p>Exclusion criteria: unclear</p> <p>Diagnostic criteria:</p> <p>FPG: 5.5 to 7.7 mmol/L</p>
Interventions	<p>Number of study centres: 9</p> <p>Run-in period: unclear</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 50 mg acarbose 3 times/d + placebo 3 times/d</p> <p>Control 1: placebo 3 times/d + placebo 3 times/d</p> <p>Control 2: 500 mg metformin 3 times/d + placebo 3 times/d</p> <p>Control 3: 500 mg metformin 3 times/d + 50 mg acarbose 3 times/d</p>
Outcomes	Composite outcome measures reported: no
Study details	<p>Trial terminated early: no</p> <p>Trial ID: ISRCTN96631607</p>
Publication details	<p>Language of publication: English</p> <p>Funding: commercial funding (Bayer and Merck-Lipha)</p> <p>Publication status: other (website, abstracts)</p>
Stated aim for study	Quote from publication: "...to determine whether deterioration in glycaemic tolerance towards diabetes can be delayed or prevented using acarbose or metformin"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: unclear
Allocation concealment (selection bias)	Unclear risk	Comment: unclear
Blinding of participants and personnel (performance bias) health-related quality of life	Unclear risk	<p>Quote: "Double-blind"</p> <p>Comment: not enough information</p>

EDIT 1997 (Continued)

Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Quote: "Double-blind" Comment: not enough information, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Quote: "Double-blind" Comment: not enough information, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-serious adverse events	Unclear risk	Quote: "Double-blind" Comment: not enough information
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) non-serious adverse events	Unclear risk	Comment: unclear
Incomplete outcome data (attrition bias) health-related quality of life	Unclear risk	Comment: unclear
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	Comment: unclear
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	Comment: unclear
Incomplete outcome data (attrition bias) non-serious adverse events	Unclear risk	Comment: unclear
Selective reporting (reporting bias)	High risk	Comment: trial was finished over 10 years ago and has still not been published
Other bias	Unclear risk	Comment: possible funding bias

Fang 2004

Methods	Parallel, 2x2 factorial RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: IGT in accordance with the diagnostic criteria of DM set by WHO in 1985</p> <p>Exclusion criteria: severe somatological disease, mental disease or history of mental disease, severe intellectual or cognitive disorders, drug or alcohol dependence</p> <p>Diagnostic criteria:</p> <p>FPG < 7.8 mmol/L and/or 2hPG of 7.8 mmol/L-11.1 mmol/L (WHO 1985)</p>
Interventions	<p>Number of study centres: single centre</p> <p>Run-in period: no</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 25-50 mg acarbose 3 times/d</p> <p>Control 1: no intervention ("common DM prevention education")</p> <p>Control 2: 125 to 250 mg flumamine (= metformin) 3 times/d</p> <p>Control 3: diet and exercise</p>
Outcomes	Composite outcome measures reported: no
Study details	<p>Trial terminated early: no</p> <p>Trial ID: -</p>
Publication details	<p>Language of publication: Chinese</p> <p>Funding: unclear</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	Quote from publication: "To observe influence of medicine intervention and non-medicine intervention on the outcomes of the crowd with impaired glucose tolerance (IGT), and explore which intervention can prevent IGT from developing to diabetes mellitus more effectively"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: trialists used random number table method, but there was baseline imbalance, which suggests randomisation was not adequate.
Allocation concealment (selection bias)	Unclear risk	Comment: not enough details
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding

Fang 2004 (Continued)

Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	Low risk	Comment: 45 completers and 5 dropouts in the treatment group, 35 completers and 5 dropouts in the no-intervention group, 44 completers and 4 dropouts in the metformin group, and 36 completers and 4 dropouts in the diet and exercise group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	Comment: 45 completers and 5 dropouts in the treatment group, 35 completers and 5 dropouts in the no-intervention group, 44 completers and 4 dropouts in the metformin group, and 36 completers and 4 dropouts in the diet and exercise group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Comment: 45 completers and 5 dropouts in the treatment group, 35 completers and 5 dropouts in the no-intervention group, 44 completers and 4 dropouts in the metformin group, and 36 completers and 4 dropouts in the diet and exercise group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other bias determined

Kawamori 2009

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	Inclusion criteria: IGT: <ul style="list-style-type: none">FPG < 6.9 mmol/L

Kawamori 2009 (Continued)

- 2hPG: 7.8-11.0 mmol/L
- HbA1c < 6.5%

≥ 1 of the following risk factors for T2DM:

- high normal blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or being treated for hypertension
- dyslipidaemia (concentrations of total cholesterol ≥ 5.7 mmol/L, triglyceride ≥ 1.7 mmol/L, or HDL cholesterol < 1.04 mmol/L)
- obesity (BMI ≥ 25 kg/m²)
- family history of diabetes (in a first-degree or second-degree relative)

Exclusion criteria: diabetes or a disease likely to impair glucose tolerance

Diagnostic criteria:

FPG < 6.9 mmol/L and 2hPG of 7.8-11.0 mmol/L ([WHO/IDF 2006](#))

HbA1c < 6.5%

Interventions	Number of study centres: 103 Japanese institutions Run-in period: 4-week observation. Moreover, "4–8 weeks before the start of treatment, each person was given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualised guidance on future lifestyle habits based on intensity of daily activity categories defined by the Japanese Ministry of Health and Labour)" Extension period: no Intervention: AGI: 0.2 mg voglibose 3 times/d Control: placebo 3 times/d Additional therapy: participants were given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualised guidance on future lifestyle habits based on intensity of daily activity categories defined by the Japanese Ministry of Health and Labour) and adherence to these was assessed at each visit.	
Outcomes	Composite outcome measures reported: no	
Study details	Trial terminated early (for benefit): yes Trial ID: UMIN000001109	
Publication details	Language of publication: English Funding: non-commercial funding Publication status: peer-reviewed journal	
Stated aim for study	Quote from publication: "We therefore investigated the effectiveness of voglibose, an α-glucosidase inhibitor that reduces diurnal insulin secretion, for prevention of the development of type 2 diabetes in Japanese patients with impaired glucose tolerance"	
Notes	-	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Kawamori 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done with a stratified allocation procedure designed to balance the two treatment groups in each institution with respect to the number of risk factors (≤ 2 or ≥ 3), which were hypertension or high normal blood pressure, dyslipidaemia, obesity, a family history of diabetes, and a 2hPG greater than 9.4 mmol/L (a concentration associated with an increased risk of developing type 2 diabetes in Japan) to 11.0 mmol/L. An independent statistician computer-generated the random sequence and this was maintained securely until the study was unmasked"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed with sealed opaque envelopes"
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Comment: double-blind, with an identical-looking placebo
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: double-blind, with an identical-looking placebo
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: double-blind, with an identical-looking placebo
Blinding of participants and personnel (performance bias) non-serious adverse events	Low risk	Comment: double-blind, with an identical-looking placebo
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	Comment: double-blind, with an identical-looking placebo
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) non-serious adverse events	Unclear risk	Comment: unclear

Kawamori 2009 (Continued)

Blinding of outcome assessment (detection bias) serious adverse events	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	High risk	Comment: 768 completers and 129 dropouts in the treatment group, 737 completers and 146 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Comment: 768 completers and 129 dropouts in the treatment group, 737 completers and 146 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Comment: 768 completers and 129 dropouts in the treatment group, 737 completers and 146 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-serious adverse events	High risk	Comment: 768 completers and 129 dropouts in the treatment group, 737 completers and 146 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) serious adverse events	High risk	Comment: 768 completers and 129 dropouts in the treatment group, 737 completers and 146 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups < 10%
Selective reporting (reporting bias)	High risk	Comment: data were not reported for some measured outcomes (FPG, HbA1c, triglycerides, total cholesterol, HDL-cholesterol, blood pressure, and body weight)
Other bias	High risk	Comment: the trial was terminated early

Koyasu 2010

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: stable angina pectoris, CAD ($\geq 50\%$ stenosis on quantitative coronary angiography), and newly diagnosed IGT or mild T2DM</p> <p>Exclusion criteria: age > 70 years, active inflammatory disease, previous treatment with antidiabetic agents, a previous diagnosis of DM, HbA1c $\geq 6.5\%$, previous cerebrovascular disease, acute coronary syndrome, renal dysfunction (serum creatinine > 1.5 mg/dL), and history or presence of cancer</p> <p>Diagnostic criteria:</p> <p>IGT: FPG < 7 mmol/L and 2hPG 7.77 to 11.05 mmol/L (WHO/IDF 2006)</p> <p>Mild T2DM: FPG < 7 mmol/L, 2hPG > 11.1 mmol/L and HbA1c < 6.5%</p>
Interventions	<p>Number of study centres: single centre</p> <p>Run-in period: no</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 50 mg acarbose 3 times/d</p>

Koyasu 2010 (Continued)

Control: no intervention

Additional therapy: participants were encouraged to exercise, stop smoking, restrict fat intake, increase dietary fibre intake, and reduce between-meal snacks

Outcomes	Composite outcome measures reported: no
Study details	Trial terminated early: no Trial ID: UMIN000000544
Publication details	Language of publication: English Funding: non-commercial funding Publication status: peer-reviewed journal
Stated aim for study	Quote from publication: "The present study examined the effect of acarbose therapy on carotid IMT in patients with established CAD who had been newly diagnosed with IGT or mild T2DM"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed using a simple sealed-envelope method" Comment: not enough information
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was performed using a simple sealed-envelope method." Comment: not enough information
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Quote: "This was a 1-year, prospective, randomised, open-label, parallel-group study..." Comment: we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Quote: "This was a 1-year, prospective, randomised, open-label, parallel-group study..." Comment: we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "This was a 1-year, prospective, randomised, open-label, parallel-group study..." Comment: we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Quote: "The primary and secondary end points were evaluated by blinded evaluators"

Koyasu 2010 (Continued)

Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote: "The primary and secondary end points were evaluated by blinded evaluators"
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "The primary and secondary end points were evaluated by blinded evaluators"
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	Low risk	Comment: 42 completers and 3 dropouts in the treatment group, 39 completers and 6 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Comment: 42 completers and 3 dropouts in the treatment group, 39 completers and 6 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: 42 completers and 3 dropouts in the treatment group, 39 completers and 6 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Selective reporting (reporting bias)	High risk	Comment: the primary outcomes in the trial register are: the incidence of cardiovascular events (defined as "new onset myocardial infarction, worsening anginal status and/or angiographic restenosis") and the carotid intima-medial thickness (IMT). In the publication the only primary outcome is the change in IMT measured in the right and left common carotid arteries. There are also differences in the secondary outcomes
Other bias	Low risk	Comment: no other bias determined

STOP-NIDDM 2002

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: men and women aged 40-70 years, with BMI of 25-40 kg/m², IGT, and FPG of 5.6-7.7 mmol/L</p> <p>Exclusion criteria: serum creatinine level ≥ 130 µmol/L, a fasting serum triglycerides ≥ 10 mmol/L, liver enzymes elevated to ≥ 1.8 times the ULN or a TSH ≥ 1.5 times above ULN or below the lower limit of normal (< 0.3 mU/L). Participants who had been treated within the last 3 months with systemic glucocorticoids, beta-blockers, thiazide diuretics, and nicotinic acid were also excluded. Key exclusion criteria were based on the use of drugs that were likely to be associated with abnormal intestinal motility or altered absorption of nutrients. All participants with a recent cardiovascular event were also excluded</p> <p>Diagnostic criteria:</p> <p>2hPG: 7.8 to 11.1 mmol/L (WHO 1985)</p> <p>FPG: 5.6 to 7.7 mmol/L</p>
Interventions	Number of study centres: multicentre

STOP-NIDDM 2002 (Continued)

Run-in period: no

Extension period: no

Intervention:

AGI: 100 mg or maximum tolerated dose acarbose 3 times/d

Control: placebo

Additional therapy: all participants were instructed to go on a weight-reduction or weight-maintenance diet and were encouraged to exercise regularly; these instructions were reinforced at each visit.

Outcomes	Composite outcome measures reported: yes, major cardiovascular events, including coronary heart disease (MI, new angina, revascularisation procedures), cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease
Study details	Trial terminated early: no Trial ID: -
Publication details	Language of publication: English Funding: commercial funding (Bayer) Publication status: peer-reviewed journal
Stated aim for study	Quote from publication: "...to assess the effect of acarbose on conversion of impaired glucose tolerance to type 2 diabetes"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a computer program to generate the random allocation sequence, which was stratified by centre. Randomisation was done in blocks of four and six"
Allocation concealment (selection bias)	Low risk	Quote: "Numbered drug containers were used to implement the random allocation process. Since the random code was stratified by center, the patients were randomized sequentially at each center. The random codes were concealed in 4-part container labels that were stored separately in the event that the investigator needed to know the treatment of a patient. The allocation sequence was generated by an independent statistician who was a member of the data safety and quality review committee"
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Comment: double-blind, with a placebo similar in size, shape and colour
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: double-blind, with a placebo similar in size, shape and colour

STOP-NIDDM 2002 (Continued)

Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: double-blind, with a placebo similar in size, shape and colour
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: double-blind, with a placebo similar in size, shape and colour
Blinding of participants and personnel (performance bias) non-serious adverse events	Low risk	Comment: double-blind, with a placebo similar in size, shape and colour
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Quote: "These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment"
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Quote: "These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment"
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote: "These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment"
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Quote: "These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment"
Blinding of outcome assessment (detection bias) non-serious adverse events	Low risk	Quote: "These events were ascertained by an independent adjudicating committee of 3 cardiologists blinded to treatment"
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	High risk	Comment: 471 completers and 211 dropouts in the treatment group, 556 completers and 130 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Comment: 471 completers and 211 dropouts in the treatment group, 556 completers and 130 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Comment: 471 completers and 211 dropouts in the treatment group, 556 completers and 130 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%

STOP-NIDDM 2002 (Continued)

Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	High risk	Comment: 471 completers and 211 dropouts in the treatment group, 556 completers and 130 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Incomplete outcome data (attrition bias) non-serious adverse events	High risk	Comment: 471 completers and 211 dropouts in the treatment group, 556 completers and 130 dropouts in the control group. Dropout rate is > 15%. Difference in dropout rates between groups > 10%
Selective reporting (reporting bias)	High risk	Comment: the definition of the outcome cardiovascular events was different in the publication (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral arterial disease) compared to the design paper (RCT, cerebrovascular accident, congestive heart failure)
Other bias	Unclear risk	Comment: possible funding bias

Wang 2000

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	Inclusion criteria: unclear Exclusion criteria: unclear Diagnostic criteria: FPG < 7.8 mmol/L and/or 2hPG of 7.8 to 11.1 mmol/L (WHO 1985)
Interventions	Number of study centres: unclear Run-in period: unclear Extension period: unclear Intervention: AGI: 50 mg acarbose 3 times/d Control: no intervention Additional therapy: participants received a minimal of 5 h training about diet to treat and prevent T2DM
Outcomes	Composite outcome measures reported: no
Study details	Trial terminated early: no Trial ID: -
Publication details	Language of publication: Chinese Funding: unclear Publication status: peer-reviewed journal

Wang 2000 (Continued)

Stated aim for study **Quote from publication:** "Observe the change of acarbose to IGT and explore the possibility of DM second class prevention"

Notes -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "divide them into 2 groups stochastically" Comment: not enough information
Allocation concealment (selection bias)	Unclear risk	Comment: unclear
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-serious adverse events	High risk	Comment: no blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) non-serious adverse events	Unclear risk	Comment: unclear
Blinding of outcome assessment (detection bias) serious adverse events	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	Comment: 30 completers and 1 dropout in the treatment group, 30 completers and no dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-serious adverse events	Low risk	Comment: 30 completers and 1 dropout in the treatment group, 30 completers and no dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) serious adverse events	Low risk	Comment: 30 completers and 1 dropout in the treatment group, 30 completers and no dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10

Wang 2000 (Continued)

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other bias determined

Yun 2016

Methods	Parallel RCT, randomisation ratio 1:1, superiority design
Participants	<p>Inclusion criteria: admission to hospital with acute coronary syndrome (ACS) and IGT. ACS was diagnosed by the presence of acute ischaemic symptoms lasting ≥ 20 min within 48 h before admission to hospital and electrocardiographic changes consistent with ACS. Acute RCT (AMI) was diagnosed when creatine kinase-muscle/brain levels increased to at least twice the ULN or when troponin T levels were > 0.1 ng/mL. Participants without AMI were considered to have unstable angina pectoris (all cases confirmed by percutaneous or computed tomography coronary angiography)</p> <p>Exclusion criteria: cardiogenic shock or pulmonary edema (Killip classification $\geq$ II) at admission; history of diabetes; history of hepatic diseases or/and renal dysfunction (serum creatinine level > 2 mg/dL); severe gastrointestinal disease or malignant tumours; female participants given sex hormone replacement therapy</p> <p>Diagnostic criteria:</p> <p>FPG < 6.1 mmol/L 2hPG: 7.8 mmol/L to 11.1 mmol/L (WHO/IDF 2006)</p>
Interventions	<p>Number of study centres: 2 centres</p> <p>Run-in period: unclear</p> <p>Extension period: no</p> <p>Intervention:</p> <p>AGI: 50 mg acarbose 3 times/d</p> <p>Control: no intervention</p> <p>Additional therapy: all participants were guided to take diet and exercise therapy, and having outpatient clinic or telephone follow-up for 1.0–4.5 years. Each group was given standard medical therapy of CAD (including nitrate medications, ACE-I/ARB, β-blockers, statins, and antiplatelet drugs)</p>
Outcomes	Composite outcome measures reported: yes, MACE: cardiovascular death, non-fatal reinfarction, new-onset angina, cerebral stroke, and severe heart failure
Study details	<p>Trial terminated early: no</p> <p>Trial ID: -</p>
Publication details	<p>Language of publication: English</p> <p>Funding: unclear</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	Quote from publication: "the goal of present study is to determine whether acarbose can reduce the risk of recurrent MACE in ACS patients with newly diagnosed IGT"
Notes	-

Yun 2016 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "135 IGT patients were randomly allocated, using random numbers generated by a computer"
Allocation concealment (selection bias)	Unclear risk	Comment: unclear
Blinding of participants and personnel (performance bias) all-cause/cardiovascular mortality	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) non-serious adverse events	High risk	Comment: no blinding
Blinding of participants and personnel (performance bias) serious adverse events	Low risk	Comment: no blinding, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause/cardiovascular mortality	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: unclear

Yun 2016 (Continued)

non-serious adverse
events

Blinding of outcome assessment (detection bias) serious adverse events	Low risk	Comment: unclear, but we judged the outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause/cardiovascular mortality	Low risk	Comment: 60 completers and 7 dropouts in the treatment group, 64 completers and 4 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Comment: 60 completers and 7 dropouts in the treatment group, 64 completers and 4 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-fatal myocardial infarction/stroke, congestive heart failure	Low risk	Comment: 60 completers and 7 dropouts in the treatment group, 64 completers and 4 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) non-serious adverse events	Low risk	Comment: 60 completers and 7 dropouts in the treatment group, 64 completers and 4 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Incomplete outcome data (attrition bias) serious adverse events	Low risk	Comment: 60 completers and 7 dropouts in the treatment group, 64 completers and 4 dropouts in the control group. Dropout rate is < 15%. Difference in dropout rates between groups < 10%
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other bias determined

"-" denotes not reported

2hPG: 2-hour plasma glucose; **ACE-I**: angiotensin-converting-enzyme inhibitor; **ACS**: acute coronary syndrome; **AGI**: alpha-glucosidase inhibitor

ARB: angiotensin II receptor blocker; **AST/ALT**: aspartate transaminase/alanine transaminase; **BMI**: body mass index; **CT**: computed tomography; **CAD**: coronary artery disease; **DAISI**: Dutch Acarbose Intervention Study in IGT; **DM**: diabetes mellitus; **ECG**: electrocardiogram; **eGFR**: estimated glomerular filtration rate; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **HDL**: high-density lipoprotein; **IGT**: impaired glucose tolerance; **LVEF**: left ventricular ejection fraction; **MACE**: major adverse cardiovascular events; **MDRD**: modification of diet and renal disease; **MI**: myocardial infarction; **NYHA**: New York Heart Association classification; **RCT**: randomised controlled trial; **rTMS**: rave Trial Management System; **T2DM**: type 2 diabetes mellitus; **TIA**: transient ischaemic attack; **TSH**: thyroid-stimulating hormone; **UA**: unstable angina; **ULN**: upper limit of normal

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
ABDOMEN study	All enrolled participants had T2DM
Aoki 2010	All enrolled participants had T2DM
EDIP	All enrolled participants had T2DM (as defined by a 2-h post-load plasma glucose ≥ 11.1 mmol/L)

Alpha-glucosidase inhibitors for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus (Review)

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Study	Reason for exclusion
JEDIS study	Trial never completed
Kataoka 2012	Population consisted of both people with T2DM and people with IGT. Attempts to contact the trial author failed (no reply)
Mangiagli 2004	Trial was not randomised
Medizinische Klinik B study	Trial never completed
MM study	All enrolled participants had T2DM
Narita 2009	All enrolled participants had T2DM
NCT00417950	Trial never completed
Toyoda 2012	All enrolled participants had T2DM
Watada 2012	All enrolled participants had T2DM
Yang 2001	No mention of randomisation in the translated manuscript. Attempts to contact the trial authors failed (emails were rejected)

EDIP: Early Diabetes Intervention Program; **JEDIS:** Japan Early Diabetes Intervention Study; **MM:** miglitol and mitiglinide; **T2DM:** type 2 diabetes

Characteristics of studies awaiting assessment [ordered by study ID]

NCT00221156

Methods	Randomised open-label clinical trial with 300 participants
Participants	Patients with abnormal glucose tolerance and recent coronary artery stents due to coronary artery disease
Interventions	Acarbose versus standard lifestyle modification
Outcomes	<p>Primary outcome: cardiovascular event free survival time</p> <p>Secondary outcomes: 1. conversion of abnormal glucose tolerance to type 2 diabetes; 2. all cause of death; 3. occurrence of every cardiovascular event; 4. occurrence of in-stent restenosis; 5. change in fasting, 2-hour blood glucose and insulin level; 6. change in homeostasis model assessment of insulin resistance; 7. change in hemoglobin A1c (HbA1c); 8. change in lipid profile</p>
Study details	<p>Trials register identifier: NCT00221156</p> <p>Official title: Effects of Acarbose Long-Term Therapy on Prevention of Cardiovascular Events in Abnormal Glucose Tolerance With Coronary Artery Disease (ALERT Study)</p> <p>Study start date: May 2005</p> <p>Actual study completion date: April 2009</p> <p>Investigators: principal investigator: Koichi Tamita, MD. Division of Cardiology, Kobe General Hospital; study director: Minako Katayama, MD Division of Clinical Research Promotion, Institute of Biomedical Research and Innovation; study director: Yutaka Furukawa, MD Division of Cardiology, Kobe General Hospital</p>
Notes	As of December 2018 there were no publications available on this trial

DATA AND ANALYSES

Comparison 1. AGI versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	4	9847	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.53, 2.90]
1.1 Acarbose	3	8069	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.18]
1.2 Voglibose	1	1778	Risk Ratio (M-H, Random, 95% CI)	12.77 [0.72, 226.31]
2 Incidence of type 2 diabetes	4	9786	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.90]
2.1 Acarbose	3	8008	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.75, 0.89]
2.2 Voglibose	1	1778	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.64]
3 Serious adverse events	3	8403	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.30]
3.1 Acarbose	2	6625	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.29]
3.2 Voglibose	1	1778	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.48, 12.62]
4 Cardiovascular mortality	4	9847	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]
4.1 Acarbose	3	8069	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.10]
4.2 Voglibose	1	1778	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.12, 72.23]
5 Non-fatal myocardial infarction	2	1486	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.53]
6 Non-fatal stroke	1	1368	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.09, 2.74]
7 Congestive heart failure	2	7890	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.21]
8 Non-serious adverse events	3	3328	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.02, 1.06]
8.1 Acarbose	2	1550	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.06]
8.2 Voglibose	1	1778	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.02, 1.10]
9 Hypoglycaemia	1	6522	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
10 Fasting plasma glucose	3	7368	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.12, -0.02]
11 2-h glucose measurements	3	6498	Mean Difference (IV, Random, 95% CI)	-0.53 [-0.92, -0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 HbA1c	3	6833	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.12, -0.05]
13 Change in total cholesterol	3	6815	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.10, 0.00]
14 Change in HDL-cholesterol	3	6807	Mean Difference (IV, Random, 95% CI)	0.01 [-0.00, 0.03]
15 Change in LDL-cholesterol	3	6699	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.07, 0.01]
16 Change in triglycerides	3	6843	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.17, 0.03]
17 Change in body weight	2	6959	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.57, 0.23]
18 Change in body mass index	2	6953	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.03]
19 Change in diastolic blood pressure	2	7452	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.78, 0.21]
20 Change in systolic blood pressure	2	7452	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.26, 0.32]

Analysis 1.1. Comparison 1 AGI versus placebo, Outcome 1 All-cause mortality.

Study or subgroup	AGI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=0.49(P=0.63)$					
Test for subgroup differences: $\chi^2=3.04$, $df=1$ ($P=0.08$), $I^2=67.11\%$					
			Favours AGI 0.002 0.1 1 10 500 Favours placebo		

Analysis 1.2. Comparison 1 AGI versus placebo, Outcome 2 Incidence of type 2 diabetes.

Study or subgroup	AGI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Acarbose					
STOP-NIDDM 2002	221/682	285/686		34.43%	0.78[0.68,0.9]
DAISI 2008	13/60	14/58		8.42%	0.9[0.46,1.74]
ACE 2017	436/3272	513/3250		35.94%	0.84[0.75,0.95]
Subtotal (95% CI)	4014	3994		78.79%	0.82[0.75,0.89]
Total events: 670 (AGI), 812 (Placebo)					
Heterogeneity: $\tau^2=0$; $\chi^2=0.81$, $df=2$ ($P=0.67$); $I^2=0\%$					
Test for overall effect: $Z=4.39$ ($P<0.0001$)					
1.2.2 Voglibose					
Kawamori 2009	50/897	106/881		21.21%	0.46[0.34,0.64]
Subtotal (95% CI)	897	881		21.21%	0.46[0.34,0.64]
Total events: 50 (AGI), 106 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=4.67$ ($P<0.0001$)					
Total (95% CI)	4911	4875		100%	0.73[0.59,0.9]
Total events: 720 (AGI), 918 (Placebo)					
Heterogeneity: $\tau^2=0.03$; $\chi^2=11.87$, $df=3$ ($P=0.01$); $I^2=74.73\%$					
Test for overall effect: $Z=2.89$ ($P=0$)					
Test for subgroup differences: $\chi^2=11.06$, $df=1$ ($P=0$), $I^2=90.96\%$					
			Favours AGI 0.1 0.2 0.5 1 2 5 10 Favours placebo		

Analysis 1.3. Comparison 1 AGI versus placebo, Outcome 3 Serious adverse events.

Study or subgroup	AGI n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Acarbose					
DAISI 2008	6/61	8/60		2.09%	0.74[0.27,2]
ACE 2017	345/3263	304/3241		97.13%	1.13[0.97,1.3]
Subtotal (95% CI)	3324	3301		99.22%	1.12[0.97,1.29]
Total events: 351 (AGI), 312 (Placebo)					
Heterogeneity: $\tau^2=0$; $\chi^2=0.68$, $df=1$ ($P=0.41$); $I^2=0\%$					
Test for overall effect: $Z=1.5$ ($P=0.13$)					
1.3.2 Voglibose					
Kawamori 2009	5/897	2/881		0.78%	2.46[0.48,12.62]
Subtotal (95% CI)	897	881		0.78%	2.46[0.48,12.62]
Total events: 5 (AGI), 2 (Placebo)					
			Favours AGI 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 1.4. Comparison 1 AGI versus placebo, Outcome 4 Cardiovascular mortality.

Analysis 1.5. Comparison 1 AGI versus placebo, Outcome 5 Non-fatal myocardial infarction.

Analysis 1.6. Comparison 1 AGI versus placebo, Outcome 6 Non-fatal stroke.

Analysis 1.7. Comparison 1 AGI versus placebo, Outcome 7 Congestive heart failure.

Analysis 1.8. Comparison 1 AGI versus placebo, Outcome 8 Non-serious adverse events.

Analysis 1.9. Comparison 1 AGI versus placebo, Outcome 9 Hypoglycaemia.

Analysis 1.10. Comparison 1 AGI versus placebo, Outcome 10 Fasting plasma glucose.

Analysis 1.11. Comparison 1 AGI versus placebo, Outcome 11 2-h glucose measurements.

Analysis 1.12. Comparison 1 AGI versus placebo, Outcome 12 HbA1c.

Analysis 1.13. Comparison 1 AGI versus placebo, Outcome 13 Change in total cholesterol.

Analysis 1.14. Comparison 1 AGI versus placebo, Outcome 14 Change in HDL-cholesterol.

Analysis 1.15. Comparison 1 AGI versus placebo, Outcome 15 Change in LDL-cholesterol.

Analysis 1.16. Comparison 1 AGI versus placebo, Outcome 16 Change in triglycerides.

Analysis 1.17. Comparison 1 AGI versus placebo, Outcome 17 Change in body weight.

Analysis 1.18. Comparison 1 AGI versus placebo, Outcome 18 Change in body mass index.

Analysis 1.19. Comparison 1 AGI versus placebo, Outcome 19 Change in diastolic blood pressure.

Analysis 1.20. Comparison 1 AGI versus placebo, Outcome 20 Change in systolic blood pressure.

Comparison 2. AGI versus metformin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Incidence of type 2 diabetes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Fasting plasma glucose	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 2-h glucose measurements	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Change in total cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Change in triglycerides	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Change in body mass index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Change in diastolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Change in systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 AGI versus metformin, Outcome 1 All-cause mortality.

Study or subgroup	AGI n/N	Metformin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fang 2004	0/50	1/48		0.32[0.01,7.67]

Analysis 2.2. Comparison 2 AGI versus metformin, Outcome 2 Incidence of type 2 diabetes.

Study or subgroup	AGI n/N	Metformin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fang 2004	6/45	9/44		0.65[0.25,1.68]

Analysis 2.3. Comparison 2 AGI versus metformin, Outcome 3 Fasting plasma glucose.

Study or subgroup	AGI N	AGI Mean(SD)	Metformin N	Metformin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fang 2004	45	-0.7 (1.7)	44	-0.4 (1.9)		-0.39[-1.14,0.36]

Analysis 2.4. Comparison 2 AGI versus metformin, Outcome 4 2-h glucose measurements.

Study or subgroup	AGI N	AGI Mean(SD)	Metformin N	Metformin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fang 2004	45	-1.4 (2)	44	0 (2.1)		-1.4[-2.25,-0.55]

Analysis 2.5. Comparison 2 AGI versus metformin, Outcome 5 Change in total cholesterol.

Study or subgroup	AGI N	AGI Mean(SD)	Metformin N	Metformin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fang 2004	45	-0.7 (1.9)	44	-1.6 (1.5)		0.9[0.19,1.61]

Analysis 2.6. Comparison 2 AGI versus metformin, Outcome 6 Change in triglycerides.

Study or subgroup	AGI		Metformin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Fang 2004	45	-0.3 (1.5)	44	-1 (2.1)		0.7 [-0.06, 1.46]
					Favours AGI Favours metformin	

Analysis 2.7. Comparison 2 AGI versus metformin, Outcome 7 Change in body mass index.

Study or subgroup	AGI		Metformin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Fang 2004	45	-0.7 (2.3)	44	-0.3 (3)		-0.4 [-1.51, 0.71]
					Favours AGI Favours metformin	

Analysis 2.8. Comparison 2 AGI versus metformin, Outcome 8 Change in diastolic blood pressure.

Study or subgroup	AGI		Metformin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Fang 2004	45	1 (7.7)	44	-5 (7.7)		6 [2.81, 9.19]
					Favours AGI Favours metformin	

Analysis 2.9. Comparison 2 AGI versus metformin, Outcome 9 Change in systolic blood pressure.

Study or subgroup	AGI		Metformin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Fang 2004	45	-6 (14.8)	44	-7 (14.8)		1 [-5.15, 7.15]
					Favours AGI Favours metformin	

Comparison 3. AGI versus diet and exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Acarbose	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Voglibose	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of type 2 diabetes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Cardiovascular mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Non-fatal myocardial infarction	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Non-fatal stroke	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Congestive heart failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Non-serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Fasting plasma glucose	2	509	Mean Difference (IV, Random, 95% CI)	-1.33 [-2.15, -0.51]
8.1 Acarbose	1	81	Mean Difference (IV, Random, 95% CI)	-1.37 [-2.24, -0.50]
8.2 Voglibose	1	428	Mean Difference (IV, Random, 95% CI)	-1.0 [-3.44, 1.44]
9 2-h glucose measurements	2	472	Mean Difference (IV, Random, 95% CI)	-2.74 [-3.74, -1.74]
9.1 Acarbose	1	81	Mean Difference (IV, Random, 95% CI)	-2.79 [-3.79, -1.79]
9.2 Voglibose	1	391	Mean Difference (IV, Random, 95% CI)	0.7 [-7.53, 8.93]
10 HbA1c	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Change in total cholesterol	2	586	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.32, 0.33]
11.1 Acarbose	1	81	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.33, 0.33]
11.2 Voglibose	1	505	Mean Difference (IV, Random, 95% CI)	0.0 [-6.47, 6.47]
12 Change in triglycerides	2	612	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.76, 0.56]
12.1 Acarbose	1	81	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.76, 0.56]
12.2 Voglibose	1	531	Mean Difference (IV, Random, 95% CI)	-0.1 [-17.03, 16.83]
13 Change in HDL-cholesterol [mmol/L]	1	545	Mean Difference (IV, Random, 95% CI)	0.0 [-2.51, 2.51]
14 Change in body mass index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Change in diastolic blood pressure	2	667	Mean Difference (IV, Random, 95% CI)	1.25 [-1.65, 4.15]
16 Change in systolic blood pressure	2	668	Mean Difference (IV, Random, 95% CI)	-1.94 [-8.71, 4.83]
16.1 Acarbose	1	81	Mean Difference (IV, Random, 95% CI)	-6.00 [-12.23, 0.23]
16.2 Voglibose	1	587	Mean Difference (IV, Random, 95% CI)	1.0 [-1.92, 3.92]

Analysis 3.1. Comparison 3 AGI versus diet and exercise, Outcome 1 All-cause mortality.

Analysis 3.2. Comparison 3 AGI versus diet and exercise, Outcome 2 Incidence of type 2 diabetes.

Analysis 3.3. Comparison 3 AGI versus diet and exercise, Outcome 3 Cardiovascular mortality.

Analysis 3.4. Comparison 3 AGI versus diet and exercise, Outcome 4 Non-fatal myocardial infarction.

Analysis 3.5. Comparison 3 AGI versus diet and exercise, Outcome 5 Non-fatal stroke.

Analysis 3.6. Comparison 3 AGI versus diet and exercise, Outcome 6 Congestive heart failure.

Study or subgroup	AGI n/N	Diet/exercise n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
ABC 2017	4/424	8/435		0.51[0.16,1.69]
Favours AGI				Favours diet/exercise

Analysis 3.7. Comparison 3 AGI versus diet and exercise, Outcome 7 Non-serious adverse events.

Study or subgroup	AGI n/N	Diet/exercise n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
ABC 2017	89/424	49/435		1.86[1.35,2.57]
Favours AGI				Favours diet/exercise

Analysis 3.8. Comparison 3 AGI versus diet and exercise, Outcome 8 Fasting plasma glucose.

Study or subgroup	AGI N	AGI Mean(SD)	Diet/exercise N	Diet/exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.8.1 Acarbose							
Fang 2004	45	-0.7 (1.7)	36	0.6 (2.2)		88.65%	-1.37[-2.24,-0.5]
Subtotal ***	45		36			88.65%	-1.37[-2.24,-0.5]
Heterogeneity: Not applicable Test for overall effect: Z=3.07(P=0)							
3.8.2 Voglibose							
ABC 2017	207	4 (12.9)	221	5 (12.9)		11.35%	-1[-3.44,1.44]
Subtotal ***	207		221			11.35%	-1[-3.44,1.44]
Heterogeneity: Not applicable Test for overall effect: Z=0.8(P=0.42)							
Total ***	252		257			100%	-1.33[-2.15,-0.51]
Heterogeneity: Tau ² =0; Chi ² =0.08, df=1(P=0.78); I ² =0% Test for overall effect: Z=3.16(P=0) Test for subgroup differences: Chi ² =0.08, df=1 (P=0.78), I ² =0%							
Favours AGI			Favours diet/exercise				

Analysis 3.9. Comparison 3 AGI versus diet and exercise, Outcome 9 2-h glucose measurements.

Study or subgroup	AGI N	AGI Mean(SD)	Diet/exercise N	Diet/exercise Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.9.1 Acarbose							
Fang 2004	45	-1.4 (2)	36	1.4 (2.5)		98.53%	-2.79[-3.79,-1.79]
Subtotal ***	45		36			98.53%	-2.79[-3.79,-1.79]
Heterogeneity: Not applicable Test for overall effect: Z=5.45(P<0.0001)							
3.9.2 Voglibose							
Favours AGI			Favours diet/exercise

Analysis 3.10. Comparison 3 AGI versus diet and exercise, Outcome 10 HbA1c.

Analysis 3.11. Comparison 3 AGI versus diet and exercise, Outcome 11 Change in total cholesterol.

Analysis 3.12. Comparison 3 AGI versus diet and exercise, Outcome 12 Change in triglycerides.

Analysis 3.13. Comparison 3 AGI versus diet and exercise, Outcome 13 Change in HDL-cholesterol [mmol/L].

Analysis 3.14. Comparison 3 AGI versus diet and exercise, Outcome 14 Change in body mass index.

Analysis 3.15. Comparison 3 AGI versus diet and exercise, Outcome 15 Change in diastolic blood pressure.

Analysis 3.16. Comparison 3 AGI versus diet and exercise, Outcome 16 Change in systolic blood pressure.

Comparison 4. AGI versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	171	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Incidence of type 2 diabetes	2	140	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.69]
3 Cardiovascular mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Non-fatal myocardial infarction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Non-fatal stroke	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Congestive heart failure	2	205	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.73]
7 Non-serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Fasting plasma glucose	3	285	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.79, 0.08]
10 2-h glucose measurements	3	285	Mean Difference (IV, Random, 95% CI)	-2.50 [-4.18, -0.83]
11 HbA1c	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
12 Change in total cholesterol	3	285	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.74, 0.10]
13 Change in HDL-cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Change in LDL-cholesterol	2	205	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.22, 0.15]
15 Change in triglycerides	3	285	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.40, -0.05]
16 Change in body weight	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Change in body mass index	3	285	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.01, -0.30]
18 Change in diastolic blood pressure	3	285	Mean Difference (IV, Random, 95% CI)	-0.26 [-3.80, 3.28]
19 Change in systolic blood pressure	3	285	Mean Difference (IV, Random, 95% CI)	-3.68 [-6.46, -0.90]

Analysis 4.1. Comparison 4 AGI versus no intervention, Outcome 1 All-cause mortality.

Study or subgroup	AGI n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fang 2004	0/50	0/40			Not estimable
Koyasu 2010	0/42	0/39			Not estimable
Total (95% CI)	92	79			Not estimable
Total events: 0 (AGI), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
<div> <div></div> <div>Favours AGI0.010.1110100Favours no intervention</div> </div>					

Analysis 4.2. Comparison 4 AGI versus no intervention, Outcome 2 Incidence of type 2 diabetes.

Analysis 4.3. Comparison 4 AGI versus no intervention, Outcome 3 Cardiovascular mortality.

Analysis 4.4. Comparison 4 AGI versus no intervention, Outcome 4 Non-fatal myocardial infarction.

Analysis 4.5. Comparison 4 AGI versus no intervention, Outcome 5 Non-fatal stroke.

Analysis 4.6. Comparison 4 AGI versus no intervention, Outcome 6 Congestive heart failure.

Analysis 4.7. Comparison 4 AGI versus no intervention, Outcome 7 Non-serious adverse events.

Analysis 4.8. Comparison 4 AGI versus no intervention, Outcome 8 Hypoglycaemia.

Analysis 4.9. Comparison 4 AGI versus no intervention, Outcome 9 Fasting plasma glucose.

Analysis 4.10. Comparison 4 AGI versus no intervention, Outcome 10 2-h glucose measurements.

Analysis 4.11. Comparison 4 AGI versus no intervention, Outcome 11 HbA1c.

Analysis 4.12. Comparison 4 AGI versus no intervention, Outcome 12 Change in total cholesterol.

Analysis 4.13. Comparison 4 AGI versus no intervention, Outcome 13 Change in HDL-cholesterol.

Analysis 4.14. Comparison 4 AGI versus no intervention, Outcome 14 Change in LDL-cholesterol.

Analysis 4.15. Comparison 4 AGI versus no intervention, Outcome 15 Change in triglycerides.

Analysis 4.16. Comparison 4 AGI versus no intervention, Outcome 16 Change in body weight.

Analysis 4.17. Comparison 4 AGI versus no intervention, Outcome 17 Change in body mass index.

Analysis 4.18. Comparison 4 AGI versus no intervention, Outcome 18 Change in diastolic blood pressure.

Analysis 4.19. Comparison 4 AGI versus no intervention, Outcome 19 Change in systolic blood pressure.

ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (design)	Intervention(s) and comparator(s)	Short description of power and sample size calculation	Screened/eligible (N)	Ran-domised (N)	ITT (N)	Analysed (N)	Finishing trial (N)	Ran-domised finishing trial (%)	Follow-up (extended follow-up) ^a
ABC 2017 (parallel RCT)	Intervention 1: vogli-bose	"Given a hazard ratio (HR) of 0.717 with survival rates of 89% at 24 months in the control group, we estimated the total sample size of 3000 subjects along with 325 events (1500 per group), providing 85% power of one-sided log-rank test of 2.5% significance level to detect the assumed reduction, assuming the loss of patients during the follow-up to be 15%"	-/870	428	424	424	424	99.1	2 years
	Comparator 1: diet and exercise			442	435	435	435	98.4	
	total:			870	859	859	859	98.7	
ACE 2017(par-allel RCT)	Intervention 1: acar-bose	"7268 patients were required with 904 adjudicated primary composite cardiovascular end points to achieve 90% power. The population size was reduced from 7500 to 6500, with an estimated 728 confirmed composite primary outcome required to have at least 85% power to detect a 20% risk reduction for acarbose, compared with placebo (two-sided $\alpha=0.05$)"	15204/7671	3272	3272	3272	3092	94.5	Median of 5 years
	Comparator 1: placebo			3250	3250	3250	3064	94.3	
	total:			6522	6522	6522	6156	94.3	
Yun 2016(par-allel RCT)	Intervention 1: acar-bose	-	426/135	67	-	60	60	89.55	1-4.5 years
	Comparator 1: no intervention			68	-	64	64	94.12	
	total:			135	-	124	124	91.85	

Table 1. Overview of trial populations (Continued)

Koyasu 2010(par- allel RCT)	Intervention 1: acar- bose	-	-/90	45	-	42	42	93.33	1 year
	Comparator 1: no in- tervention			45	-	39	39	86.67	
	total:			90	-	81	81	90	
Kawamori 2009(par- allel RCT)	Intervention 1: vogli- bose	"Assuming a conversion rate of 7.7% per year, a study duration of 4.9 years, and a drop-out rate of 5%, the planned sample size was 864 (90% power to detect a 40% reduction in the primary endpoint with a two-sided type I error of 0.05). Due to greater improvement to normoglycaemia than expected, sample size increased to 1728"	4582/1780	897	-	897	768	85.62	Until di- agnosis of normogly- caemia or diabetes type 2, or at least 3 years
	Comparator 1: place- bo			883	-	881	737	83.47	
	total:			1780	-	1778	1505	84.55	
Fang 2004(par- allel RCT)	Intervention 1: acar- bose	-	-/-	50	-	45	45	90	5 years
	Comparator 1: no in- tervention			40	-	35	35	87.5	
	Comparator 2: met- formin			48	-	44	44	91.67	
	Comparator 3: diet and exercise			40	-	36	36	90	
	total:			178	-	160	160	89.89	
Wang 2000(par- allel RCT)	Intervention 1: acar- bose	-	-/61	31	-	30	30	96.77	1 year
	Comparator 1: No in- tervention			30	-	30	30	100	
	total:			61	-	60	60	98.36	

Table 1. Overview of trial populations (Continued)

DAISI 2008(par- allel RCT)	Intervention 1: acar- bose	47 participants in each treatment group with alpha (2-sided) = 0.05 and beta = 0.05	6651/118	60	60	60	30	50	3 years
	Comparator 1: place- bo			p8	58	58	36	62.07	
	total:			118	118	118	66	55.93	
EDIT 1997(fac- torial RCT)	Intervention 1: acar- bose + placebo	-	-/631	157	-	-	-	-	6 years
	Comparator 1: place- bo + placebo			159	-	-	-	-	
	Comparator 2: met- formin + placebo			160	-	-	-	-	
	Comparator 3: met- formin + acarbose			155	-	-	-	-	
	total:			631	-	-	522	82.73	
STOP- NIDDM 2002(par- allel RCT)	Intervention 1: acar- bose	"It was estimated that 600 patients would be required in each treat- ment group for a 2-tailed alpha of .05 and a 1-beta of 90% assum- ing a conversion rate of 7% per year, a 36% risk reduction, and a drop-out rate of 10%"	14742/1429	714	682	682	471	65.97	mean 3.3 years
	Comparator 1: place- bo			715	686	686	556	77.76	
	total:			1429	1368	1368	1027	71.87	
Grand to- tal	All interventions			5721			4962 (ex- cl. EDIT 1997)		
	All comparators			6093			5076 (ex- cl. EDIT 1997)		
	All interventions and comparators			11,814			10,038 (excl. EDIT 1997)		

10,560
(incl. [EDIT](#)
1997)

Table 1. Overview of trial populations *(Continued)*

- denotes not reported; **ITT**: intention-to-treat; **RCT**: randomised controlled trial

^aFollow-up under randomised conditions until end of trial (= duration of intervention + follow-up post-intervention or identical to duration of intervention); extended follow-up refers to follow-up of participants once the original trial was terminated as specified in the power calculation.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL; via Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Prediabetic state
 2. MESH DESCRIPTOR Glucose Intolerance
 3. (prediabet* or pre diabet*):TI,AB,KY
 4. (intermediate hyperglyc?emi*):TI,AB,KY
 5. ((impaired fasting ADJ2 glucose) or IFG or impaired FPG):TI,AB,KY
 6. glucose intolerance:TI,AB,KY
 7. ((impaired glucose ADJ (tolerance or metabolism)) or IGT):TI,AB,KY
 8. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) ADJ4 (diabetes or T2D* or NIDDM or "type 2" or "type II")):TI,AB,KY
 9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
 10. MESH DESCRIPTOR Acarbose
 11. (acarbos* or glucobay or precose or prandase or "bay g 5421" or BAYG5421):TI,AB,KY
 12. (voglibos* or glustat or basen or "A 71100" or "AO 128"):TI,AB,KY
 13. (miglitol* or glyset or "BAY m 1099" or "Bay 1099"):TI,AB,KY
 14. (glucosidase* ADJ3 inhibitor*):TI,AB,KY
 15. #10 OR #11 OR #12 OR #13 OR #14
 16. 9 AND 15
-

MEDLINE (Ovid SP)

1. Prediabetic state/
 2. Glucose Intolerance/
 3. (prediabet* or pre diabet*).tw.
 4. intermediate hyperglyc?emi*.tw.
 5. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.
 6. glucose intolerance.tw.
 7. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.
 8. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.
 9. or/1-8
 10. Acarbose/
 11. (acarbos* or glucobay or precose or prandase or "bay g 5421" or BAYG5421).tw.
-

(Continued)

12. (voglibos* or glustat or basen or "A 71100" or "AO 128").tw.

13. (miglitol* or glyset or "BAY m 1099" or "Bay 1099").tw.

14. (glucosidase* adj3 inhibitor*).tw.

15. or/10-14

16. 9 and 15

[17-27: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

17. randomized controlled trial.pt.

18. controlled clinical trial.pt.

19. randomi?ed.ab.

20. placebo.ab.

21. drug therapy.fs.

22. randomly.ab.

23. trial.ab.

24. groups.ab.

25. or/17-24

26. exp animals/ not humans/

27. 25 not 26

28. 16 and 27

[29: Wong 2006a- systematic reviews filter - SensSpec version]

29. meta analysis.mp,pt. or review.pt. or search*.tw.

30. 16 and 29

31. 28 or 30

Embase (Ovid SP)

1. (prediabet* or pre diabet*).tw.

2. intermediate hyperglyc?emi*.tw.

3. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.

4. glucose intolerance.tw.

5. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.

6. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) ADJ4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.

7. or/1-6

8. exp alpha glucosidase inhibitor/

9. (acarbos* or glucobay or precose or prandase or "bay g 5421" or BAYG5421).tw.

10. (voglibos* or glustat or basen or "A 71100" or "AO 128").tw.

(Continued)

11. (miglitol* or glyset or "BAY m 1099" or "Bay 1099").tw.

12. (glucosidase* adj3 inhibitor*).tw.

13. or/8-12

14. 7 and 13

[15: [Wong 2006b](#) "sound treatment studies" filter - SDSSGS version]

15. random*.tw. or clinical trial*.mp. or exp treatment outcome/

16. 14 and 15

[17-20: TSC filter for exclusion of animal references]

17. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

18. human/ or normal human/ or human cell/

19. 17 and 18

20. 17 not 19

21. 16 not 20

22. conference.pt.

23. 21 not 22

ICTRP Search Portal (Standard search)

acarbos* OR glucobay OR precose OR prandase OR bay g 5421 OR BAYG5421 OR voglibos* OR glustat OR basen OR A 71100 OR AO 128 OR miglitol* OR glyset OR BAY m 1099 OR Bay 1099 OR glucosidase inhibitor*

(Records from ClinicalTrials.gov were deleted from results retrieved by this search, as this trials register was searched separately. Number of results reported for this resource include the ClinicalTrials.gov records.)

ClinicalTrials.gov (Expert search)

(prediabetes OR prediabetic OR "pre diabetes" OR "pre diabetic" OR "intermediate hyperglycemia" OR "intermediate hyperglycaemia" OR "intermediate hyperglycemic" OR "intermediate hyperglycaemic" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "glucose intolerance" OR IGT OR IFG OR ((diabetes OR "type 2" OR "type II" OR T2D OR T2DM) AND (risk OR progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR develop OR delay OR delayed OR prevention OR prevent OR prevented))) AND ("glucosidase inhibitor" OR "glucosidases inhibitor" OR "inhibitor of alpha glucosidase" OR "inhibitor of alpha glucosidases" OR acarbose OR "bay g 5421" OR BAYG5421 OR glucobay OR precose OR prandase OR voglibose OR glustat OR basen OR "A 71100" OR "AO 128" OR miglitol OR glyset OR "BAY m 1099" OR "Bay 1099")

Appendix 2. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included trial, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person per-

(Continued)

formed this who was not otherwise involved in the trial. We will consider the use of the minimisation technique as equivalent to being random.

- Unclear risk of bias: insufficient information about the sequence generation process
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We described for each included trial the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
- Unclear risk of bias: insufficient information about the allocation concealment
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure

We also evaluated trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias ([Corbett 2014](#)).

Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between trials that we rated as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judged as being at low risk of bias on the basis of baseline similarity alone ([Corbett 2014](#)). We reclassified judgements of unclear, low or high risk of selection bias as specified in [Appendix 3](#).

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)

We evaluated the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We noted whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judged that the outcome was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We evaluated the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We noted whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judged that the outcome measurement was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included trial or each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the trial reported attrition and exclusions, and reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

(Continued)

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference), among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents (Appendix 8)' (Boutron 2014; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we could not enter them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias

- Low risk of bias: the trial appeared to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials reporting unadjusted analyses - comparison of results obtained using method details alone with results using method details and trial baseline information^a

Reported randomisation and allocation concealment methods	'Risk of bias' judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk

(Continued)

		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly random, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk

^aTaken from [Corbett 2014](#); judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone

^bImbalance identified which appears likely to be due to chance

^cDetails for the remaining important prognostic variables not reported

Appendix 4. Description of interventions

Trial ID	Intervention(s) (route, frequency, total dose/day)	Comparator(s) (route, frequency, total dose/day)
ABC 2017	Voglibose (3 times/d, 0.6 mg/d) In the event of gastrointestinal adverse effects the dosage was reduced to half or a quarter of the original dosage.	Diet and exercise
ACE 2017	Acarbose (3 times/d, 150 mg/d)	Placebo (3 times/d)
Yun 2016	Acarbose (3 times/d, 75 mg/d start, gradually increased to 150 mg/d in two weeks)	No intervention
Koyasu 2010	Acarbose (150 mg/d)	No intervention
Kawamori 2009	Voglibose (3 times/d, 0.6 mg/d)	Placebo (3 times/d)

(Continued)

Fang 2004	Acarbose (3 times/d, 75-150 mg/d)	<ol style="list-style-type: none"> 1. No intervention (common diabetes prevention education) 2. Flumamine (= metformin) (3 times/d, 375-750 mg/d) 3. Diet and exercise (education and dietary advice and exercise based on personal situation)
Wang 2000	Acarbose (3 times/d, 150 mg)	No intervention
DAISI 2008	Acarbose (week 1: once/d, 50 mg/d; week 2: 2 times/d, 100 mg/d; week 3-endpoint: 3 times/d, 150 mg/d)	Placebo (week 1: once/d; week 2: 2 times/d; week 3-endpoint: 3 times/d)
EDIT 1997	Acarbose (3 times/d, 150 mg/d) + placebo (3 times/d)	<ol style="list-style-type: none"> 1. Placebo (3 times/d) + placebo (3 times/d) 2. Metformin (3 times/d, 1500 mg/d) + placebo (3 times/d) 3. Metformin (3 times/d, 1500 mg/d) + acarbose (50 mg 3 times/d)
STOP-NIDDM 2002	Acarbose (start 3 times/d, 150 mg/d; end 3 times/d, 300 mg/d or maximum tolerated dose)	Placebo

Appendix 5. Baseline characteristics (1)

Trial ID	Intervention(s) and comparator(s)	Duration of intervention/duration of follow-up ^a	Description of participants (diagnostic criteria)	Trial period (year to year)	Country	Setting	Ethnic groups (%)
ABC 2017	Intervention: voglibose	2 years/2 years	Clinically overt MI	2005-2012	Japan	-	-
	Comparator: diet and exercise		FPG $\leq$ 7.0 mmol/L 2hPG: 7.8-11.1 mmol/L HbA1c: $\leq$ 6.5%				
ACE 2017	Intervention: acarbose	Median of 5 years/median of 5 years	Coronary heart disease	2009-2015	China	Outpatients	Han Chinese: 97% Other: 3%
	Comparator: placebo		FPG $<$ 7.0 mmol/L 2hPG $\geq$ 7.8 and $<$ 11.1 mmol/L				Han Chinese: 97% Other: 3%
Yun 2016	Intervention: acarbose	1-4.5 years/1-4.5 years	ACS	2010-2016	China	Outpatients	-
	Comparator: no intervention		FPG $<$ 6.1 mmol/L 2hPG $\geq$ 7.8 mmol/L and $<$ 11.1 mmol/L				
Koyasu 2010	Intervention: acarbose	1 year/1 year	Stable angina pectoris, CAD	2006-2009	Japan	Outpatients	-
	Comparator: no intervention		IGT: FPG $<$ 7 mmol/L 2hPG $\geq$ 7.77 and $<$ 11.05 mmol/L Mild T2DM: FPG $<$ 7 mmol/L, 2hPG $>$ 11.1 mmol/L HbA1c $<$ 6.5%				
Kawamori 2009	Intervention: voglibose	Until diagnosis of normoglycaemia or T2DM, or at least 3 years/until	BMI $\geq$ 25 kg/m ²	2003-2007	Japan	Outpatients	-
	Comparator: placebo		T2DM as risk factor				

(Continued)

		diagnosis of normoglycaemia or T2DM, or at least 3 years	FPG < 6.9 mmol/L 2hPG ≥ 7.8 mmol/L and < 11.0 mmol/L, HbA1c < 6.5%				
Fang 2004	Intervention: acarbose	5 years/5 years	FPG < 7.8 mmol/L and/or 2hPG ≥ 7.8 and < 11.1	1998-2002	China	-	-
	Comparator 1: no intervention						
	Comparator 2: metformin						
	Comparator 3: diet and exercise						
Wang 2000	Intervention: acarbose	1 year/1 year	FPG < 7.8 mmol/L 2hPG ≥ 7.8 and < 11.1	-	China	-	-
	Comparator: no intervention						
DAISI 2008	Intervention: acarbose	3 years/3 years	FPG < 7.8 mmol/L 2hPG: 7.8–11.1 mmol/L HbA1c ≤ 7.0%	1996-2000	The Netherlands	Outpatients	-
	Comparator: placebo						
EDIT 1997	Intervention: acarbose + placebo	6 years/6 years	FPG: 5.5-7.7 mmol/L	1997-2003	UK	-	94% White
	Comparator 1: placebo + placebo						
	Comparator 2: metformin + placebo						
	Comparator 3: metformin + acarbose						
STOP-NIDDM 2002	Intervention: acarbose	Mean 3.3 years/ mean 3.3 years	BMI: 25-40 kg/m ² FPG: 5.6-7.7 mmol/L 2hPG ≥ 7.8 and < 11.1 mmol/L	1995-1998	Canada, Germany, Austria, the Nordic countries, Israel and Spain	Outpatients	97% White 98% White
	Comparator: placebo						

- denotes not reported

(Continued)

^aFollow-up under randomised conditions until end of trial (= duration of intervention + follow-up post-intervention or identical to duration of intervention)

2hPG: 2-hour plasma glucose; **ACS:** acute coronary syndrome; **BMI:** body mass index; **CAD:** coronary artery disease; **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **IGT:** impaired glucose tolerance; **MI:** myocardial infarction; **T2DM:** type 2 diabetes mellitus

Appendix 6. Baseline characteristics (2)

Trial ID	Intervention(s) and comparator(s)	Sex (female %)	Age (mean/range years (SD))	Blood pressure (mean mmHg (SD), range)	Access to health care, social determinants
ABC 2017	Intervention: voglibose	14	67 (57-73)	Diastolic: 73 (68-80) Systolic: 126 (114-136)	-
	Comparator: diet and exercise	13	65 (58-73)	Diastolic: 72 (66-80) Systolic: 124 (114-136)	-
ACE 2017	Intervention: acarbose	27	64.4 (8.2)	Diastolic: 78 (9) Systolic: 130 (14)	-
	Comparator: placebo	27	64.3 (8)	Diastolic: 78 (9) Systolic: 129 (14)	-
Yun 2016	Intervention: acarbose	42	62.2 (5.2)	Diastolic: 94 (7) Systolic: 150 (10)	-
	Comparator: no intervention	38	61.6 (4.6)	Diastolic: 93 (5) Systolic: 149 (9)	-
Koyasu 2010	Intervention: acarbose	10	66.1 (8.6)	-	-
	Comparator: no intervention	8	66.5 (8)	-	-
Kawamori 2009	Intervention: voglibose	40	55.7 (9.1)	-	-
	Comparator: placebo	40	55.7 (9.2)	-	-
Fang 2004	Intervention: acarbose	44	50 (7)	Diastolic: 82 (7) Systolic: 130 (14)	-
	Comparator 1: no intervention	45	47 (14)	Diastolic: 84 (6) Systolic: 128 (13)	-
	Comparator 2: metformin	46	50 (7)	Diastolic: 85 (7) Systolic: 132 (14)	-
	Comparator 3: diet and exercise	45	49 (6)	Diastolic: 86 (6) Systolic: 126 (13)	-
Wang 2000	Intervention: acarbose	48	64 (8.7)	-	-
	Comparator: no intervention	47	63 (7)	-	-

(Continued)

DAISI 2008	Intervention: acarbose	51	58.5 (7.9)	Diastolic: 90 (13) Systolic: 147 (18)	-
	Comparator: placebo	50	56.5 (7)	Diastolic: 90 (10) Systolic: 147 (18)	-
EDIT 1997	Intervention: acarbose + placebo	R: 51	R: 52.1 (10)	-	-
	Comparator 1: placebo + placebo			-	-
	Comparator 2: metformin + placebo			-	-
	Comparator 3: metformin + acarbose			-	-
STOP-NIDDM 2002	Intervention: acarbose	52	54.3 (7.9)	Diastolic: 83 (9) Systolic: 131 (16)	-
	Comparator: placebo	50	54.6 (7.9)	Diastolic: 82 (9.) Systolic: 131 (16)	-

- denotes not reported

IGT: impaired glucose tolerance; **R**: randomised; **SD**: standard deviation

Appendix 7. Baseline characteristics (3)

Trial ID	Intervention(s) and comparator(s)	Fasting plasma glucose (mean mmol/L (SD))	2-hour plasma glucose (mean mmol/L (SD))	HbA1c (%)	BMI (mean kg/m ² (SD), range)	Comedications/Cointerventions (N (%))	Comorbidities (N (%))
ABC 2017	Intervention: voglibose	-	9.1	5.5 (5.2-5.7)	24.2 (22.5-26.0)	β-blockers: 209 (50.6); ACE inhibitors: 133 (32.2); ARBs: 165 (40.0); CCBs: 122 (29.5); Anti-hyperlipidaemia therapy: 336 (81.4); Anti-platelet therapy: 382 (92.5); Anti-coagulant therapy: 37 (9.6); Diuretics: 78 (18.9)	Hypertension: 300 (72.6); Dyslipidemia: 324 (78.5); Stroke: 25 (6.1); Arteriosclerosis obliterans: 11 (2.7)
	Comparator: diet and exercise	-	9.2	5.5 (5.2-5.7)	24.3 (22.5-26.2)	β-blockers: 204 (47.2); ACE inhibitors: 136 (31.5); ARBs: 208 (48.1); CCBs: 118 (27.3); Anti-hyperlipidaemia therapy: 348 (80.6); Anti-platelet therapy: 417 (96.5); Anti-coagulant therapy: 36 (8.6); Diuretics: 82 (19.0)	Hypertension: 311 (72.0); Dyslipidemia: 334 (77.3); Stroke: 26 (6.0); Arteriosclerosis obliterans: 12 (2.8)
ACE 2017	Intervention: acarbose	5.5 (0.9)	9.3 (1.1)	5.9 (0.8)	25.3 (3.1)	β-blockers: 2141 (66) ACE inhibitors/ARBs: 1930 (59) CCBs: 967 (30) Nitrates: 1191 (36) Statins: 3038 (93) Fibrate: 35 (1)	Previous MI: 1350 (41) Previous unstable angina: 1352 (41) Current stable angina: 727 (22)

(Continued)

						Niacin: 13 (<1) Any antiplatelet therapy: 3198 (98) Aspirin: 3063 (94) Clopidrogel: 2000 (61) Other: 40 (1)	
	Comparator: placebo	5.5 (0.8)	9.3 (1.1)	5.9 (0.7)	25.5 (3.1)	β-blockers: 2160 (66) ACE inhibitors/ARBs: 1909 (59) CCBs: 938 (29) Nitrates: 1217 (37) Statins: 3028 (93) Fibrate: 32 (1) Niacin: 9 (<1) Any antiplatelet therapy: 3186 (98) Aspirin: 3063 (94) Clopidrogel: 1983 (61) Other: 38 (1)	Previous MI: 1350 (41) Previous unstable angina: 1352 (41) Current stable angina: 727 (22)
Yun 2016	Intervention: acarbose	5.9 (0.4)	9.0 (0.5)	6.3 (0.3)	26.1 (3.2)	β-blockers: 13 (19.40) ACE inhibitors: 45 (67.16) CCBs: 20 (29.85) Statin; 61 (91.04) Aspirin: 62 (92.54)	Previous MI: 1362 (42) Previous unstable angina: 1363 (42) Current stable angina: 690 (21)
	Comparator: no intervention	5.8 (0.3)	8.8 (0.5)	6.3 (0.2)	25.8 (2.5)	β-blockers: 16 (23.53) ACE inhibitors: 47 (69.12) CCBs: 18 (26.47) Statin: 63 (92.65) Aspirin: 64 (94.12)	AMI: 43 (63.24) Revascularisation: 38 (55.88)
Koyasu 2010	Intervention: acarbose	6.0 (0.6)	10.7 (2.0)	5.6 (0.4)	24.9 (2.7)	β-blockers: 13 (31.0) ACE inhibitors/ARBs: 25 (59.5) CCBs: 25 (59.5) Statins: 40 (95.2) Aspirin: 41 (97.6) Diuretics: 3 (7.1)	Hypertension: 40 (95.2) Previous MI: 18 (42.9)
	Comparator: no intervention	6.0 (1.0)	10.4 (2.8)	5.6 (0.4)	24.5 (3.3)	β-blockers: 17 (43.6) ACE inhibitors/ARBs: 25 (64.1) CCBs: 19 (48.7)	Hypertension: 36 (92.3) Previous MI: 20 (51.3)

(Continued)

							Statins: 38 (97.4) Aspirin: 35 (89.7) Diuretics: 5 (12.8)
Kawamori 2009	Intervention: voglibose	5.8 (0.6)	9.1 (0.9)	-	25.8 (3.7)	-	Obesity: 502 (55.96) Dyslipidaemia: 695 (77.48) Hypertension: 528 (58.86)
	Comparator: placebo	5.9 (0.6)	9.1 (0.9)	-	25.9 (3.8)	-	Obesity: 500 (56.75) Dyslipidaemia: 667 (75.71) Hypertension: 510 (57.89)
Fang 2004	Intervention: acarbose	6.5 (1.9)	8.4 (1.9)	-	24.9 (2.1)	-	-
	Comparator 1: no intervention	5.7 (2.3)	6.4 (2.2)	-	24.8 (2.5)	-	-
	Comparator 2: metformin	6.3 (2.1)	7.5 (1.9)	-	25.2 (2.8)	-	-
	Comparator 3: diet and exercise	5.6 (2.4)	7.0 (2.1)	-	25.3 (1.9)	-	-
Wang 2000	Intervention: acarbose	-	-	5.0 (1.3)	22.7 (3.4)	-	-
	Comparator: no intervention	-	-	5.2 (1.2)	21.0 (3.0)	-	-
DAISI 2008	Intervention: acarbose	6.6 (0.5)	9.6 (0.7)	5.9 (0.5)	28.4 (3.9)	-	-
	Comparator: placebo	6.5 (0.6)	9.5 (0.7)	5.6 (0.6)	29.5 (3.8)	-	-

(Continued)

EDIT 1997	Intervention: acarbose + placebo	R: 6.0 (0.5)	-	R: 5.9 (0.5)	R: 28.6 (4.5)	-	-
	Comparator 1: placebo + placebo					-	-
	Comparator 2: metformin + placebo					-	-
	Comparator 3: metformin + acarbose					-	-
STOP-NIDDM 2002	Intervention: acarbose	6.2 (0.5)	9.3 (1.1)	-	31.0 (4.3)	Cardiovascular medication: 146 (21.4)	Hypertension: 357 (52) Dyslipidemia: 395 (59) History of cardiovascular disease: 34 (5.0)
	Comparator: placebo	6.2 (0.5)	9.3 (1.0)	-	30.9 (4.2)	Cardiovascular medication: 138 (20.1)	Hypertension: 345 (50) Dyslipidemia: 394 (57) History of cardiovascular disease: 32 (4.7)

- denotes not reported

^aFollow-up under randomised conditions until end of trial (= duration of intervention + follow-up post-intervention or identical to duration of intervention)

ACE: angiotensin-converting enzyme; **AMI:** acute myocardial infarction; **ARB:** angiotensin II receptor blocker; **BMI:** body mass index; **C:** comparator; **CCBs:** calcium channel blockers; **HbA1c:** glycosylated haemoglobin A1c; **IGT:** impaired glucose tolerance; **MI:** myocardial infarction; **R:** randomised; **SD:** standard deviation

Appendix 8. Matrix of trial endpoints (publications and trial documents)

Trial ID	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper) ^a	Trial results available in trial register Yes/No	Endpoints quoted in publication(s) ^{b,c}	Endpoints quoted in abstract of publication(s) ^{b,c}
ABC 2017	<p>Source: NCT00212017</p> <p>Primary outcome measure(s):</p> <ol style="list-style-type: none"> 1. Cardiovascular mortality 2. Hospitalisation due to cardiovascular events <hr/> <p>Secondary outcome measure(s):</p> <ol style="list-style-type: none"> 1. All-cause mortality 2. Hospitalisation due to coronary artery disease 3. Progression of IGT to diabetes 4. Development or deterioration of either hypertension or hyperlipidaemia 5. Deterioration of renal function 6. Hospitalisation due to cerebrovascular disease 7. Hospitalisation due to heart failure <hr/> <p>Other outcome measure(s): -</p> <hr/> <p>History of changes: last change 8 November 2007</p>	No	<p>Primary outcome measure(s): "The primary outcome was the time until the first cardiovascular composite endpoint of death from cardiovascular death, and hospitalization due to non-fatal MI, non-fatal unstable angina, non-fatal stroke, or treatment with coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft)"</p> <hr/> <p>Secondary outcome measure(s): "Secondary outcomes were death from cardiovascular disease, non-fatal MI, non-fatal unstable angina, treatment with coronary revascularization, non-fatal stroke, death from any cause, and hospitalization for HF"</p> <hr/> <p>Other outcome measure(s): -</p>	<p>Primary outcome measure(s): "The primary endpoint was cardiovascular events including cardiovascular death, non-fatal MI, non-fatal unstable angina, non-fatal stroke, and percutaneous coronary intervention/coronary artery bypass graft"</p> <hr/> <p>Secondary outcome measure(s): "Secondary endpoints included individual components of the primary endpoint in addition to all-cause mortality and hospitalization due to heart failure"</p> <hr/> <p>Other outcome measure(s): -</p>
ACE 2017	<p>Source: design paper (Holman 2014 under ACE 2017), ISRCTN91899513 and NCT00829660</p> <p>Primary outcome measure(s):</p> <p>Design paper: "The primary composite cardiovascular outcome is the time to the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke."</p> <p>Clinical Study Protocol</p> <p>ICTRP:</p>	No	<p>Primary outcome measure(s): "The original primary composite cardiovascular outcome, a three-point major cardiovascular adverse event (MACE) outcome (first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was expanded to a five-point MACE to also include hospital admission for unstable angina and hospital admission for heart failure."</p>	<p>Primary outcome measure(s): "The primary outcome was a five-point composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure."</p>

(Continued)

"Current primary outcome measure as of 20/04/2018:
Major cardiovascular events (defined as: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure [MACE5]) occurring after randomisation (baseline) were identified through patient interviews at study visits, physician and/or family member reports and by searches of local or national electronic health records, death registries, or other publicly available sources (where permitted by local ethics approvals). All events were adjudicated by an independent Clinical Events Committee, blinded to therapy allocation.

Previous primary outcome measures as of 01/08/2017:

A composite cardiovascular outcome defined as the time after randomisation to the first occurrence of any one of the following:

1. Cardiovascular death
2. Non-fatal MI
3. Non-fatal stroke
4. Hospitalisation for unstable angina
5. Hospitalisation for heart failure

Previous primary outcome measures:
Occurrence of any one of the following:

1. Cardiovascular death
2. Non-fatal MI
3. Non-fatal stroke"

ClinicalTrials.gov

1. A composite cardiovascular outcome defined as the time after randomisation to the first occurrence of any one of the following: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina, hospitalisation for heart failure (time frame: follow-up until 728 adjudicated primary outcome measures have been recorded)

mission for heart failure"

Secondary outcome measure(s):

Design paper: "Secondary end points include new-onset diabetes, all-cause mortality, and an extended composite cardiovascular end point consisting of the primary composite cardiovascular end point plus hospitalization for heart failure or hospitalization for unstable angina. Each component of this composite will also be analysed individually. Other secondary end points are: propor-

Secondary outcome measure(s): "The original three-point MACE became a secondary outcome. The other prespecified secondary outcomes were all-cause death; cardiovascular death; non-fatal myocardial infarction; non-fatal stroke; hospital admission for unstable angina; hospital admission for heart fail-

Secondary outcome measure(s): "The secondary outcomes were a three-point composite outcome (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke).

(Continued)

tion of patients with possible evidence of non-alcoholic fatty liver disease as judged by changes in ALT levels; proportion of patients with impaired renal function, i.e., eGFR <30 mL/min per 1.73 m² using the Chinese MDRD formula, doubling of baseline plasma creatinine, or halving of baseline eGFR." "number, type, and, dose of medications including trial therapy; number of hospital clinic visits; and in-patient hospitalizations associated with complications/adverse events. The duration of hospitalizations will be recorded, and whether the patient underwent angiography, angioplasty, coronary artery bypass grafting or other major procedures"

ICTRP:

"Current secondary outcome measures as of 20/04/2018:

1. Individual MACE5 components and all-cause mortality were ascertained as for the primary outcome measure.
2. Transition to type 2 diabetes was ascertained from four-monthly study visit fasting plasma glucose values and by annual study visit 75g oral glucose tolerance tests, or by non-study physician reports adjudicated by an independent Clinical Events Committee, blinded to therapy allocation.
3. Transition to impaired renal function (defined as: eGFR <30 mL/min/1.73 m², doubling of baseline serum creatinine concentration, or halving of baseline eGFR) was ascertained from annual study visit plasma creatinine measurements.
4. Medical resource use data were collected at 4-monthly study visits.

Previous secondary outcome measures as of 01/08/2017:

1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG =7.0 mmol/L and/or 2hr PG =11.1 mmol/L), with no intervening non-diagnostic values.
2. All-cause mortality.
3. Each of the components of the primary composite cardiovascular outcome will also be analysed individually, both as first and as total events.
4. MACE composite cardiovascular outcome, defined as the time after randomisation to the first occurrence of any one of the following:
 - Cardiovascular death
 - Non-fatal MI

ure; the proportion of participants developing diabetes, as confirmed by two successive diagnostic plasma glucose values (defined as fasting plasma glucose ≥126 mg/dL [≥7.0 mmol/L] or 2 h plasma glucose ≥200 mg/dL [≥11.1 mmol/L]) with no intervening non-diagnostic values, or diagnosed outside of the study; and the proportion of participants developing impaired renal function (defined as one or more of the following criteria: eGFR <30 mL/min per 1.73 m², doubling of baseline serum creatinine concentration, or halving of baseline eGFR). To avoid confounding by competing mortality risks, we have chosen to report fatal or non-fatal myocardial infarction and fatal or non-fatal stroke as post-hoc secondary endpoints, rather than non-fatal myocardial infarction and non-fatal stroke as originally planned. Additional secondary outcomes were resource use, cost, and cost effectiveness; these health-economic outcomes will be reported elsewhere"

death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, development of diabetes, and development of impaired renal function"

(Continued)

- Non-fatal stroke
- 5. Proportion of patients with an impaired renal function as evidenced by:
 - A reduced eGFR (<30 ml/minute/ 1.73 m²) estimated using the Chinese MDRD formula
 - A doubling of the baseline plasma creatinine level
 - A halving of the baseline eGFR.
- 6. Resource use, costs and cost effectiveness.

Previous as of 02/03/10:

1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG = 7.0 mmol/L and/or 2hPG = 11.1 mmol/L), with no intervening non-diagnostic values
2. All cause mortality
3. Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure or hospitalisation for unstable angina. Each of the components of this composite will also be analysed individually, both as first and as total events.
4. Proportion of patients with evidence of non-alcoholic fatty liver disease (NAFLD) as judged by changes in ALT levels
5. Proportion of patients with an impaired renal function as evidenced by: A reduced eGFR (<30 ml/minute/ 1.73 m²) estimated using the Chinese MDRD formula, or a doubling of the baseline plasma creatinine level, or a halving of the baseline eGFR"

ClinicalTrials.gov:

- 1. Transition to type 2 diabetes confirmed by two successive diagnostic plasma glucose values (FPG >7.0 mmol/L and/or 2hr PG > 11.1 mmol/L), with no intervening non-diagnostic values
- 2. All cause mortality
- 3. Each of the components of the primary composite cardiovascular outcome will also be analysed individually, both as first and as total events
- 4. Major Cardiovascular Event (MACE) composite cardiovascular outcome, defined as the time after randomisation to the first occurrence of any one of the following: cardiovascular death, non-fatal MI, non-fatal stroke
- 5. Impaired renal function as evidenced by: a reduced estimate of glomerular filtration rate(eGFR <30

(Continued)

ml/minute/ 1.73 m²) estimated using the Chinese MDRD formula, a doubling of the baseline plasma creatinine level, a halving of the baseline eGFR

- 6. Resource use, costs and cost effectiveness

Other outcome measure(s): "Blood pressure and fasting plasma glucose (FPG) are recorded every 4 months with serum alanine aminotransferase, serum creatinine, lipid profile, haemoglobin A1c, and full blood counts measured annually by the local laboratory in each center. Annual electrocardiograms (ECGs) are recorded and Hepatitis B antigenicity status noted where available. [...] OGTTs are performed annually. " "...adverse events that lead to a change in dose or discontinuation of study medication are recorded. Only serious adverse events that do not equate to study end points are reported urgently to the China Food and Drug Administration"

Other outcome measure(s): "...measure fasting plasma glucose, record hypoglycaemic episodes, blood pressure, and body-weight; ascertain clinical outcomes; and monitor study medication adherence." "Alanine aminotransferase concentrations, measured annually for safety, were reviewed unmasked by the data and safety monitoring board. At annual visits, patients did oral glucose tolerance tests, had HbA1c and serum creatinine measured, and had estimated glomerular filtration rate (eGFR) calculated by use of the Modification of Diet in Renal Disease study equation, adapted for a Chinese population." "....serious adverse events thought to be possible study endpoints were not reported as serious adverse events, although any other serious adverse events were reported to the sponsor and the China Food and Drug Administration (CFDA) according to the relevant regulations. [...] adverse events were recorded when study medication was reduced or stopped as a result, or the event was thought to be related to study medication"

Other outcome measure(s): -

History of changes: last change 21 July 2017 (ClinicalTrials.gov)

Yun 2016

Source: N/T

Primary outcome measure(s): "The carotid IMT was measured at baseline, and follow-up of all subjects [...] Incidence of MACE (including fatal cardiovascular events, non-fatal reinfarction, new-onset angina,

Primary outcome measure(s): "the incidence of major adverse cardiovascular event (MACE) and carotid intima-middle thick-

(Continued)

			cerebral stroke, and severe heart failure) was recorded"	ness (CIMT) were statistically analyzed"
			Secondary outcome measure(s): "...biochemical indicators, [...] blood pressure, and BMI."	Secondary outcome measure(s): -
			Other outcome measure(s): -	Other outcome measure(s): -
Koyasu 2010	Source: UMIN000000544			
	Primary outcome measure(s): "incidence of cardiovascular events: new onset myocardial infarction, worsening anginal status and/or angiographic restenosis. Carotid intima-medial thickness(IMT)"		Primary outcome measure(s): "the absolute change from baseline to 12 months in the largest measured IMT value in the right and left common carotid arteries"	Primary outcome measure(s): "Carotid IMT was measured by ultrasonography at baseline and at 12 months of follow-up."
	Secondary outcome measure(s): "1-1) Ultrasonic echo cardiography (IVS; Interventricular Septal Thickness, EF; Ejection Fraction, E/A, LVDd; Left Ventricular Diastolic dimension) 2-1) HbA1c 2-2) IRI 2-3) blood glucose levels 2-4) HOMA-R, HOMA-beta 3) Plasma lipid profile"		Secondary outcome measure(s): "the change from baseline to 12 months in glucose profiles (OGTT), HbA1c, and lipid profiles." Clinical data: "The data of interest included the incidence of death, non-fatal myocardial infarction, repeat percutaneous coronary intervention for a treated coronary artery, and stroke"	Secondary outcome measure(s): "The changes in glucose profiles (75-g OGTT), HbA1c and lipid profiles were also compared between baseline and follow-up." "Clinical follow-up data on outcomes of interest were obtained from patients' hospital charts or from telephone interviews; these outcomes were the incidence of mortality, non-fatal myocardial infarction, repeat percutaneous coronary intervention for a treated coronary artery, and stroke"
	Other outcome measure(s): -		Other outcome measure(s): -	Other outcome measure(s): -
Kawamori 2009	Source: UMIN000001109	No	Primary outcome measure(s): "The primary endpoint was the development of type 2 diabetes"	Primary outcome measure(s): develop-

(Continued)

	Primary outcome measure(s): "Progression from IGT to type 2 diabetes mellitus."		ment of type 2 diabetes
	Secondary outcome measure(s): -	Secondary outcome measure(s): "The secondary endpoint was the number of people who achieved normoglycaemia" "...fasting blood glucose, HbA1c, blood lipids (triglycerides, total cholesterol, HDL cholesterol, and free fatty acids), [...] blood pressure and body weight, [...] adverse effects"	Secondary outcome measure(s): normoglycaemia, adverse events
	Other outcome measure(s): -	Other outcome measure(s): -	Other outcome measure(s): -
	History of changes: -		
Fang 2004	Source: N/T	Primary outcome measure(s): diabetes mellitus incidence	Primary outcome measure(s): incidence of diabetes mellitus
		Secondary outcome measure(s): "fasting plasma glucose (FPG), postprandial 2-hour glucose, body height, body mass index (BMI), blood pressure and blood lipid"	Secondary outcome measure(s): "The fasting plasma glucose (FPG), postprandial 2-hour glucose, body height, body mass index (BMI), blood pressure and blood lipid were examined every half year"
		Other outcome measure(s): -	Other outcome measure(s): -
Wang 2000	Source: N/T	Primary outcome measure(s): incidence of IGT, NGT and diabetes mellitus	Primary outcome measure(s): incidence of IGT, NGT and diabetes mellitus
		Secondary outcome measure(s): -	Secondary outcome measure(s): -
		Other outcome measure(s): -	Other outcome measure(s): -

(Continued)

DAISI 2008	Source: study protocol and NTR150	No	Primary outcome measure(s): "We defined the primary outcome measure as the plasma glucose level 2 h after oral intake of 75-g glucose after 3 years of treatment"	Primary outcome measure(s): "2-h plasma glucose level and beta-cell function"
			Secondary outcome measure(s): "Fasting [...] plasma glucose levels were measured [...] Plasma-specific insulin (mU/L) was measured [...] and intact proinsulin [...] Total cholesterol, HDL cholesterol, and triglycerides were measured." "We estimated beta-cell function" "Rate of conversion to diabetes according to the former WHO criterion"	Secondary outcome measure(s): -
			Other outcome measure(s): -	Other outcome measure(s): -
History of changes: last change 15 May 2008				
EDIT 1997	Source: protocol EDIT website , ISRCTN96631607	No	Primary outcome measure(s): -	Primary outcome measure(s): incidence of type 2 diabetes
			Secondary outcome measure(s): "beta cell function, insulin sensitivity, lipid profiles, biochemical risk factors, body weight, microalbuminuria, retinopathy, digital electrocardiography and quality of life."	Secondary outcome measure(s): "side effects, weight, clinical and biochemical outcomes"

(Continued)

	Other outcome measure(s): -		Other outcome measure(s): -	Other outcome measure(s): -
STOP-NIDDM 2002	<p>Source: design paper (Chiasson 1998 under STOP-NIDDM 2002)</p> <p>Primary outcome measure(s): "The primary outcome is the development of diabetes type 2 based on a 75-g oral glucose tolerance test (OGTT)"</p>	No	<p>Primary outcome measure(s): "The primary endpoint was development of diabetes, defined as a plasma glucose concentration 11.1 mmol/L or greater 2 h after 75 g glucose based on one oral glucose tolerance test (OGTT)"</p>	<p>Primary outcome measure(s): "The primary endpoint was development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT)"</p> <p>Chiasson 2003 (under STOP-NIDDM 2002):</p> <p>"Main Outcome Measures: The development of major cardiovascular events (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral arterial disease) and hypertension"</p>
	<p>Secondary outcome measure(s): improvement in glucose tolerance, the effect of the treatment on baseline insulin, insulin sensitivity, anthropometric measures, cardiovascular events (myocardial infarction, cerebrovascular accident, congestive heart failure), nutritional evaluations, HbA1c, serum insulin, total cholesterol and triglycerides, HDL and LDL cholesterol, blood pressure, lipid profile</p>		<p>Secondary outcome measure(s): improvement in glucose tolerance, plasma insulin, anthropometric measures, nutritional evaluations, HbA1c, serum insulin, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, blood pressure, lipid profiles; adverse events</p>	<p>Secondary outcome measure(s): -</p>
	<p>Other outcome measure(s): -</p>		<p>Other outcome measure(s): Chiasson 2003 (under STOP-NIDDM 2002): "We acknowledge the limitations in the interpretation of the cardiovascular data from the STOP-NIDDM trial. First, the intent-to-treat population is modified by excluding the 61 patients whose post-randomization data was unavailable because they had dropped out of the study immediately af-</p>	<p>Other outcome measure(s): reversion of impaired glucose tolerance to normal glucose tolerance, side effects</p>

(Continued)

ter being randomized without taking any study medications. Second, the study was powered for incidence of diabetes, not for CVD, which was an a priori secondary objective"

- denotes not reported

^aTrial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).

^bPublication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial).

^cPrimary and secondary outcomes refer to verbatim specifications in publication/records. Other outcome measures refer to all outcomes not specified as primary or secondary outcome measures.

2hPG: 2-hour plasma glucose; **ALT:** alanine transaminase; **BMI:** body mass index; **CVD:** cardiovascular disease; **eGFR:** estimated glomerular filtration rate; **EMA:** European Medicines Agency; **FDA:** Food and Drug Administration (US); **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **HDL:** high-density lipoprotein; **HF:** heart failure; **ICRTP:** International Clinical Trials Registry Platform; **IGT:** impaired glucose tolerance; **IMT:** intima-middle thickness; **MACE:** major adverse cardiovascular event; **MI:** myocardial infarction; **MDRD:** modification of diet in renal disease; **NGT:** normal glucose tolerance; **N/T:** no trial document available; **OGTT:** oral glucose tolerance test; **LDL:** low-density lipoprotein; **UMIN:** University hospital Medical Information Network

Appendix 9. High risk of outcome reporting bias according to ORBIT classification

Trial ID	Outcome	High risk of bias (category A) ^a	High risk of bias (category D) ^b	High risk of bias (category E) ^c	High risk of bias (category G) ^d
ABC 2017	Progression of IGT to T2DM	No	Yes	No	No
ACE 2017	N/A				
Yun 2016	N/A				
Koyasu 2010	N/A				
Kawamori 2009	Fasting plasma glucose	No	No	Yes	No
	HbA1c	No	No	Yes	No
	Triglycerides	No	No	Yes	No
	Total cholesterol	No	No	Yes	No
	HDL-cholesterol	No	No	Yes	No
	Blood pressure	No	No	Yes	No
	Body weight	No	No	Yes	No
Fang 2004	N/A				

(Continued)

Wang 2000 N/A

DAISI 2008 N/A

EDIT 1997 N/A

STOP-NIDDM 2002 N/A

^aClear that outcome was measured and analysed; trial report states that outcome was analysed but reports only that result was not significant (Classification 'A', table 2, [Kirkham 2010](#)).

^bClear that outcome was measured and analysed; trial report states that outcome was analysed but reports no results (Classification 'D', table 2, [Kirkham 2010](#)).

^cClear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results (Classification 'E', table 2, [Kirkham 2010](#)).

^dUnclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results (Classification 'G', table 2, [Kirkham 2010](#)).

HbA1c: glycosylated haemoglobin A1c; **HDL**: high-density lipoprotein; **IGT**: impaired glucose tolerance; **N/A**: not applicable; **ORBIT**: Outcome Reporting Bias In Trials; **ST2DM**: type 2 diabetes mellitus

Appendix 10. Definition of endpoint measurement (1)^a

Trial ID	All-cause mortality	Incidence of type 2 diabetes	Serious adverse events	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Congestive heart failure	Amputation of lower extremity
ABC 2017	"Death from any cause" (AO)	N/I	Additional adverse events not detected as primary or secondary endpoints (AO)	"Cardiovascular death" (AO)	"Nonfatal myocardial infarction" (AO)	"Nonfatal stroke" (AO)	"Heart failure" (AO)	N/I
ACE 2017	"All-cause death" (IO)	"Two successive diagnostic plasma glucose values (defined as fasting plasma glucose ≥ 126 mg/dL [≥ 7.0 mmol/L] or 2 h plasma glucose ≥ 200 mg/dL [≥ 11.1 mmol/L]) with no intervening non-diagnostic values, or diagnosed outside of the study" (AO)	Serious adverse events were reported if it was not a possible endpoint (IO)	"Cardiovascular death" (AO)	N/I	N/I	"Hospital admission for heart failure" (IO)	N/I
Yun 2016	N/I	N/I	N/D	Fatal cardiovascular events (IO)	Non-fatal reinfarction (IO)	Cerebral stroke (IO)	Severe heart failure (IO)	N/I
Koyasu 2010	Deaths (IO)	N/I	N/D (IO and SO)	N/D	Non-fatal myocardial infarction (IO)	Stroke (IO)	Congestive heart failure (IO)	N/I
Kawamori 2009	Deaths (IO)	"Type 2 diabetes, which was defined as an HbA1c level of at least 6.5%, and, on two separate occasions, at least one of the following: a 2hPG of at least 11.1 mmol/L, fasting plasma glucose concentration of at least 7.0 mmol/L, or random plasma glucose concentration of at least 11.1 mmol/L" (IO)	"Serious adverse events" (IO)	N/D (IO)	N/I	N/I	N/I	N/I
Fang 2004	Deaths (IO)	"In accordance with the diagnostic criteria of DM set by WHO in 1985" (IO)	N/I	N/I	N/I	N/I	N/I	N/I

(Continued)

Wang 2000	N/I	According to the diagnostic criteria of diabetes mellitus by WHO in 1985 (IO)	N/I	N/I	N/I	N/I	N/I	N/I
DAISI 2008	Deaths (IO)	FPG $\geq$ 7.8 mmol/L 2hPG $\geq$ 11.1 mmol/L (IO)	"Serious adverse event" (IO)	N/D (IO)	N/D (IO)	N/I	N/I	N/I
EDIT 1997	N/I	N/D	N/D	N/I	N/I	N/I	N/I	N/I
STOP-NID-DM 2002	Deaths (IO)	2hPG $\geq$ 11.1 mmol/L based on an OGTT (IO)	N/D	"Cardiovascular death was death due to congestive heart failure, myocardial infarction, cerebrovascular event, cardiovascular procedures, pulmonary embolism, or sudden death" (IO)	"Clinical symptoms of myocardial ischemia with elevated serum cardiac enzymes and electrocardiographic changes; at least 2 of 3 criteria had to be present for the clinical diagnosis" (IO)	"Cerebrovascular events related to the presence of neurological deficits such as transient ischemic attack or stroke" (IO)	"Congestive heart failure was defined as recent onset of new or aggravation of symptoms compatible with heart failure with supportive documentation such as chest radiograph or electrocardiographic changes" (IO)	N/I

^aIn addition to definition of endpoint measurement, description of who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement)

2hPG: 2-hour plasma glucose; **DM**: diabetes mellitus; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **ICH-GCP**: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice; **N/D**: not defined; **N/I**: not investigated; **OGTT**: oral glucose tolerance test; **SAE**: serious adverse event; **T2DM**: type 2 diabetes mellitus

Appendix 11. Definition of endpoint measurement (2)^a

Trial ID	Blindness or severe vision loss	End-stage renal disease	Non-serious adverse events	Hypoglycaemic events	Health-related quality of life	Time to progression to T2DM	Measures of blood glucose control	Socioeconomic effects
ABC 2017	N/I	N/I	"Additional adverse events not detected as primary or secondary endpoints" (AO)	N/I	N/I	N/I	"75-g OGTT, HbA1c level" (AO)	N/I
ACE 2017	N/I	N/I	"Adverse events were recorded when study medication was reduced or stopped as a result, or the event was thought to be related to study medication." (IO)	"Hypoglycaemic episodes" (IO)	N/I	N/I	FPG, 2hPG, HbA1c (IO)	N/I
Yun 2016	N/I	N/I	N/D	N/D	N/I	N/I	FPG, 2hPG, HbA1c (IO)	N/I
Koyasu 2010	N/I	N/I	N/D (IO and SO)	N/I	N/I	N/I	FPG, 2hPG (IO)	N/I
Kawamori 2009	N/I	N/I	Adverse events (SO)	N/I	N/I	N/I	FPG, 2hPG, HbA1c (IO)	N/I
Fang 2004	N/I	N/I	N/I	N/I	N/I	N/I	FPG, 2hPG (IO)	N/I
Wang 2000	N/I	N/I	N/D	N/I	N/I	N/I	2hPG (IO)	N/I
DAISI 2008	N/I	N/I	Adverse events (SO)	N/I	N/I	N/I	FPG and 2hPG levels were measured with a hexokinase method (Boehringer, Mannheim, Germany) (IO)	N/I
EDIT 1997	N/I	N/I	N/D	N/I	N/D	N/I	FPG, HbA1c, 2hPG (IO)	N/I
STOP-NID-DM 2002	N/I	N/I	Adverse events (SO)	N/I	N/I	N/I	FPG, 2hPG (glucose oxidase and hexokinase method), HbA1c (HPLC) (IO)	N/I

^aIn addition to definition of endpoint measurement, description who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement)

(Continued)

2hPG: 2-hour plasma glucose; **DM:** diabetes mellitus; **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **HPLC:** high-performance liquid chromatography; **N/D:** not defined; **N/I:** not investigated; **OGTT:** oral glucose tolerance test; **T2DM:** type 2 diabetes mellitus

Appendix 12. Adverse events (1)

Trial ID	Intervention(s) and comparator(s)	Partici- pants in- cluded in analysis (N)	Deaths (N)	Deaths (% of par- ticipants)	Partici- pants with at least one adverse event (N)	Partici- pants with at least one adverse event (%)	Partici- pants with at least one severe/seri- ous adverse event (N)	Partici- pants with at least one severe/seri- ous adverse event (%)
ABC 2017	Intervention: voglibose	424	11	2.6	89	21.0	-	-
	Comparator: diet and exercise	435	6	1.4	49	11.3	-	-
ACE 2017	Intervention: acarbose	3272	216	6.6	-	-	345	10.5
	Comparator: placebo	3250	219	6.7	-	-	304	9.4
Yun 2016	Intervention: acarbose	60	-	-	-	-	-	-
	Comparator: no intervention	64	-	-	-	-	-	-
Koyasu 2010	Intervention: acarbose	42	0	0	-	-	-	-
	Comparator: no intervention	39	0	0	-	-	-	-
Kawamori 2009	Intervention: voglibose	897	6	0.7	810	90.0	5	0.6
	Comparator: placebo	881	0	0	750	85.0	2	0.2
Fang 2004	Intervention: acarbose	50	0	0	-	-	-	-
	Comparator 1: no intervention	40	0	0	-	-	-	-
	Comparator 2: metformin	48	1	2.1	-	-	-	-
	Comparator 3: diet and exercise	40	0	0	-	-	-	-
Wang 2000	Intervention: acarbose	30	-	-	2	6.7	0	0
	Comparator: no intervention	30	-	-	0	0	0	0
DAISI 2008	Intervention: acarbose	61	1	1.7	53	86.9

(Continued)

	Comparator: placebo	60	3	5.2	48	80.0		
EDIT 1997	Intervention: acarbose + placebo	R: 631	-	-	-	-	-	-
	Comparator 1: placebo + placebo		-	-	-	-	-	-
	Comparator 2: metformin + placebo		-	-	-	-	-	-
	Comparator 3: metformin + acarbose		-	-	-	-	-	-
STOP-NID-DM 2002	Intervention: acarbose	714	6	0.8	698	97.8	-	-
	Comparator: placebo	715	3	0.4	675	94.4	-	-
- denotes not reported								
IGT: impaired glucose tolerance; N: number of participants; R: randomised								

Appendix 13. Adverse events (2)

Trial ID	Intervention(s) and comparator(s)	Partici- pants in- cluded in analysis (N)	Partici- pants dis- continuing trial due to an adverse event (N)	Partici- pants dis- continuing trial due to an adverse event (%)	Partici- pants with at least one hospitalisa- tion (N)	Partici- pants with at least one hospitalisa- tion (%)	Partici- pants with at least one outpatient treatment (N)	Partici- pants with at least one outpatient treatment (%)
ABC 2017	Intervention: voglibose	424	-	-	-	-	-	-
	Comparator: diet and exercise	435	-	-	-	-	-	-
ACE 2017	Intervention: acarbose	3272	52	1.6	-	-	-	-
	Comparator: placebo	3250	50	1.5	-	-	-	-
Yun 2016	Intervention: acarbose	60	6	9.0	-	-	-	-
	Comparator: no intervention	64	0	0	-	-	-	-
Koyasu 2010	Intervention: acarbose	42	2	4.8	4	9.5	-	-
	Comparator: no intervention	39	0	0	4	10.3	-	-
Kawamori 2009	Intervention: voglibose	897	62	7.0	-	-	-	-
	Comparator: placebo	881	55	6.0	-	-	-	-
Fang 2004	Intervention: acarbose	50	-	-	-	-	-	-
	Comparator 1: no intervention	40	-	-	-	-	-	-
	Comparator 2: metformin	48	-	-	-	-	-	-
	Comparator 3: diet and exercise	40	-	-	-	-	-	-
Wang 2000	Intervention: acarbose	30	-	-	-	-	-	-
	Comparator: no intervention	30	-	-	-	-	-	-
DAISI 2008	Intervention: acarbose	61	22	36.1	-	-	-	-

(Continued)

	Comparator: placebo	60	8	13.3	-	-	-	-
EDIT 1997	Intervention: acarbose + placebo	R: 631	-	-	-	-	-	-
	Comparator 1: placebo + placebo		-	-	-	-	-	-
	Comparator 2: metformin + placebo		-	-	-	-	-	-
	Comparator 3: metformin + acarbose		-	-	-	-	-	-
STOP-NID-DM 2002	Intervention: acarbose	714	136	19.0	-	-	-	-
	Comparator: placebo	715	37	5.0	-	-	-	-

- denotes not reported

IGT: impaired glucose tolerance; **N:** number of participants; **R:** randomised

Appendix 14. Adverse events (3)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse event (N)	Participants with at least one specific adverse event (%)
ABC 2017	Intervention: voglibose	424	(1) Gastrointestinal disorders	(1) 36	(1) 8.5
			(2) Hepatic disorders	(2) 7	(2) 1.7
			(3) Benign and malignant disorders	(3) 8	(3) 1.9
			(4) Metabolic and nutritional disorders	(4) 6	(4) 1.4
			(4.5) Hypoglycemia	(4.5) 3	(4.5) 0.7
			(5) Nervous system disorders	(5) 6	(5) 1.4
			(6) Infectious disorders	(6) 7	(6) 1.7
			(7) Renal and urinary disorders	(7) 2	(7) 0.5
			(8) Cardiac disorders	(8) 5	(8) 1.2
			(9) Vascular disorders	(9) 2	(9) 0.5
	Comparator: diet and exercise	435	(1) Gastrointestinal disorders	(1) 3	(1) 0.7
			(2) Hepatic disorders	(2) 2	(2) 0.5
			(3) Benign and malignant disorders	(3) 3	(3) 0.7
			(4) Metabolic and nutritional disorders	(4) 0	(4) 0
			(4.5) Hypoglycemia	(4.5) 0	(4.5) 0
			(5) Nervous system disorders	(5) 5	(5) 1.1
			(6) Infectious disorders	(6) 7	(6) 1.6
			(7) Renal and urinary disorders	(7) 1	(7) 0.2
			(8) Cardiac disorders	(8) 13	(8) 3.0
			(9) Vascular disorders	(9) 6	(9) 1.4
ACE 2017	Intervention: acarbose	3272	(1) Benign, malignant and unspecified neoplasms	(1) 85	(1) 3
			(2) Infections and infestations	(2) 70	(2) 2
			(3) Gastrointestinal disorders	(3) 76	(3) 2
			(4) Vascular disorders	(4) 47	(4) 1
			(5) Nervous system disorders	(5) 37	(5) 1
			(6) Musculoskeletal and connective tissue disorders	(6) 30	(6) 1
			(7) Adverse events (gastrointestinal disorders)	(7) 215	(7) 7
	Comparator: placebo	3250	(1) Benign, malignant and unspecified neoplasms	(1) 88	(1) 2
			(2) Infections and infestations	(2) 74	(2) 2
			(3) Gastrointestinal disorders	(3) 59	(3) 2

(Continued)

			(4) Vascular disorders	(4) 36	(4) 1
			(5) Nervous system disorders	(5) 26	(5) 1
			(6) Musculoskeletal and connective tissue disorders	(6) 21	(6) 1
			(7) Adverse events (gastrointestinal disorders)	(7) 150	(7) 5
Yun 2016	Intervention: acarbose	60	-	-	-
	Comparator: no intervention	64	-	-	-
Koyasu 2010	Intervention: acarbose	42	-	-	-
	Comparator: no intervention	39	-	-	-
Kawamori 2009	Intervention: voglibose	897	(1) Flatulence	(1) 156	(1) 17
			(2) Abdominal distension	(2) 120	(2) 13
			(3) Diarrhea	(3) 110	(3) 13
			(4) Constipation	(4) 39	(4) 4
			(5) Abnormal bowel sounds	(5) 39	(5) 4
			(6) Gastrointestinal discomfort	(6) 10	(6) 1
			(7) Upper abdominal pain	(7) 4	(7) < 1
	Comparator: placebo	881	(1) Flatulence	(1) 63	(1) 7
			(2) Abdominal distension	(2) 49	(2) 5
			(3) Diarrhea	(3) 45	(3) 5
			(4) Constipation	(4) 22	(4) 2
			(5) Abnormal bowel sounds	(5) 11	(5) 1
			(6) Gastrointestinal discomfort	(6) 6	(6) < 1
			(7) Upper abdominal pain	(7) 4	(7) < 1
Fang 2004	Intervention: acarbose	50	-	-	-
	Comparator 1: no intervention	40	-	-	-
	Comparator 2: metformin	48	-	-	-
	Comparator 3: diet and exercise	40	-	-	-
Wang 2000	Intervention: acarbose	30	-	-	-

(Continued)

	Comparator: no intervention	30	-	-	-
DAISI 2008	Intervention: acarbose	61	(1) Digestive	(1) 37	(1) 60.7
			(2) Flatulence	(2) 27	(2) 44.3
	Comparator: placebo	60	(1) Digestive	(1) 10	(1) 16.7
			(2) Flatulence	(2) 2	(2) 3.3
EDIT 1997	Intervention: acarbose + placebo	R: 631	-	-	-
	Comparator 1: placebo + placebo		-	-	-
	Comparator 2: metformin + placebo		-	-	-
	Comparator 3: metformin + acarbose		-	-	-
STOP-NIDDM 2002	Intervention: acarbose	714	(1) Gastrointestinal	(1) 597	(1) 83
			(2) Flatulence	(2) 486	(2) 68
			(3) Diarrhea	(3) 229	(3) 32
			(4) Abdominal pain	(4) 125	(4) 17
			(5) Dyspepsia	(5) 53	(5) 7
			(6) Nausea	(6) 36	(6) 5
			(7) Constipation	(7) 27	(7) 4
			(8) Gastroenteritis	(8) 31	(8) 4
			(9) Gastritis	(9) 18	(9) 3
	Comparator: placebo	715	(1) Gastrointestinal	(1) 426	(1) 60
			(2) Flatulence	(2) 196	(2) 27
			(3) Diarrhea	(3) 123	(3) 17
			(4) Abdominal pain	(4) 89	(4) 12
			(5) Dyspepsia	(5) 62	(5) 9
			(6) Nausea	(6) 39	(6) 5
			(7) Constipation	(7) 35	(7) 5
			(8) Gastroenteritis	(8) 36	(8) 5
			(9) Gastritis	(9) 19	(9) 3

(Continued)

- denotes not reported

IGT: impaired glucose tolerance; **N:** number of participants; **R:** randomised

Appendix 15. Adverse events (4)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with at least one hypoglycaemic episode (N)	Participants with at least one hypoglycaemic episode (%)
ABC 2017	Intervention: voglibose	424	-	-
	Comparator: diet and exercise	435	-	-
ACE 2017	Intervention: acarbose	3272	421	12.9
	Comparator: placebo	3250	416	12.8
Yun 2016	Intervention: acarbose	60	-	-
	Comparator: no intervention	64	-	-
Koyasu 2010	Intervention: acarbose	42	-	-
	Comparator: no intervention	39	-	-
Kawamori 2009	Intervention: voglibose	897	-	-
	Comparator: placebo	881	-	-
Fang 2004	Intervention: acarbose	50	-	-
	Comparator 1: no intervention	40	-	-
	Comparator 2: metformin	48	-	-
	Comparator 3: diet and exercise	40	-	-
Wang 2000	Intervention: acarbose	30	-	-
	Comparator: no intervention	30	-	-
DAISI 2008	Intervention: acarbose	61	-	-
	Comparator: placebo	60	-	-
EDIT 1997	Intervention: acarbose + placebo	R: 631	-	-
	Comparator 1: placebo + placebo		-	-
	Comparator 2: metformin + placebo		-	-

(Continued)

	Comparator 3: metformin + acarbose	-	-
STOP-NIDDM 2002	Intervention: acarbose	714	-
	Comparator: placebo	715	-

- denotes not reported

IGT: impaired glucose tolerance; **N:** number of participants; **R:** randomised

Appendix 16. Survey of trial investigators providing information on included trials

Trial ID	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
ABC 2017	24 December 2017	27 December 2017	24 December 2017 Requested additional unpublished data	12 January 2018 Received the unpublished data
ACE 2017	14 November 2017	14 November 2017	14 November 2017 Requested published data	14 November 2017 Received the published data
	21 November 2017		21 November 2017 Requested additional unpublished data	6 December 2017 Received the unpublished data
Yun 2016	15 April 2017	No answer	15 April 2017 Requested any additional published or unpublished data	N/A
Koyasu 2010	15 April 2017	26 April 2017	15 April 2017 Requested any additional published or unpublished data	26 April 2017 They sent the protocol and mentioned that the raw data were lost
Kawamori 2009	7 April 2017	No answer	7 April 2017 Requested any additional published or unpublished data	N/A
Fang 2004	14 June 2006	20 June 2006	20 June 2006 Requested a reprint of the article	20 June 2006 They sent the article in Chinese with an English abstract
Wang 2000	14 June 2005	No answer	14 June 2005 Requested additional data from the study	N/A

(Continued)

DAISI 2008	14 September 2004 18 April 2017	20 June 2005 11 May 2017	14 September 2004 Requested any additional published or unpublished data 18 April 2017 Requested additional unpublished data.	20 June 2005 The author sent the study report 11 May 2017 They could not find the additional data: raw data we were missing
EDIT 1997	6 October 2004 30 May 2017	31 January 2005 1 June 2017	6 October 2004 Requested any unpublished or published data 30 May 2017 Requested any unpublished or published data	6 October 2004 As they had not published their data yet, they did not send their data 1 June 2017 The author replied that the publication is still a work in progress
STOP-NIDDM 2002	14 September 2004	9 November 2005	14 September 2004 Requested unpublished data	9 November 2005 Provided answers and unpublished data
N/A: not applicable				

Appendix 17. Checklist to aid consistency and reproducibility of GRADE assessments (acarbose versus placebo)

		(1) All-cause mortality	(2) Incidence of T2DM	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke/congestive heart failure	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias)^a	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	Yes	Yes	Yes/Yes/Yes	N/A	N/A
	Was allocation concealment used (i.e. no potential for selection bias)?	Yes	Yes	Yes	Yes	Yes/Yes/Yes		
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes/Yes/Yes		
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes/Yes/Yes		
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes/Yes/Yes		
	Were > 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^b	Yes	Yes	Yes	Yes	No (↓)/No (↓)/Yes		
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes	Yes	Yes	No (↓)/No (↓)/Yes		
	No other biases reported (i.e. no potential of other bias)?	No (↓)	No (↓)	No (↓)	No (↓)	Yes/Yes/No (↓)		
Inconsistency^c	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes	Yes	Yes/Yes/Yes		
	Point estimates did not vary widely?	Yes	Yes	Yes	Yes	Yes/N/A/Yes		

(Continued)

	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	Substantial	Substantial	Substantial	Substantial	Substantial/ N/A/Substantial
	Was the direction of effect consistent?	No (↓)	Yes	Yes	No (↓)	Yes/ N/A /Yes
	What was the magnitude of statistical heterogeneity (as measured by I ² statistic) - low (I ² < 40%), moderate (I ² 40%-60%), high I ² > 60%)?	Low	Low	Low	Low	Low/ N/A /Low
	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant	Not statistically significant	Not statistically significant	Not statistically significant	Not statistically significant/ N/A /Not statistically significant
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable?	Highly applicable?	Highly applicable?	Highly applicable?	Highly applicable/Highly applicable/Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable/Highly applicable/Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes/Yes/Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient/Sufficient/Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes/Yes/Yes

(Continued)

Imprecision^d	Was the confidence interval for the (pooled) estimate not consistent with benefit and harm?	No (↓)	Yes	No (↓)	No (↓)	Yes/(No (↓))/No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)? ^b	High	High	High	High	High/High/High
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5-10 studies, small: < 5 studies)? ^b	Small (↓)	Small (↓)	Small (↓)	Small (↓)	Small (↓)/Small (↓)/ Small (↓)
	Was the outcome a common event (e.g. occurs > 1/100)?	Yes	Yes	Yes	Yes	Yes / No (↓) / Yes
Publication bias^e	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes/Yes/Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes/Yes/Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes/Yes/Yes
	There was no industry influence on studies included in the review?	Unclear	Unclear	Unclear	Unclear	Unclear/Unclear/Unclear
	There was no evidence of funnel plot asymmetry?	N/A	N/A	N/A	N/A	N/A / N/A / N/A
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear	Unclear	Unclear/Unclear/Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials.

^bDepends on the context of the systematic review area.

^cQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2 statistic.

^dWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful.

^eQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

(↓): key item for potentially downgrading the quality of the evidence (GRADE) as shown in the footnotes of [Summary of findings for the main comparison](#); **N/A**: not applicable; **T2DM**: type 2 diabetes mellitus

Appendix 18. Checklist to aid consistency and reproducibility of GRADE assessments (acarbose versus no intervention)

		(1) All-cause mortality	(2) Incidence of T2DM	(3) Serious adverse events	(4) Cardio-vascular mortality	(5) Non-fatal myocardial infarction/stroke/congestive heart failure	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias)^a	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	N/A	Unclear	Unclear/Unclear/Unclear	N/A	N/A
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear		Unclear	Unclear/Unclear/Unclear		
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes/Yes/Yes		
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes		Yes	Yes/Yes/Yes		
	Was an objective outcome used?	Yes	Yes		Yes	Yes/Yes/Yes		
	Were > 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^b	Yes	Yes		Yes	Yes/Yes/Yes		
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Unclear	Unclear		Yes	Yes/Yes/Yes		
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes		Yes	Yes/Yes/Yes		
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes		Yes	Yes/Yes/Yes		
Inconsistency^c	Point estimates did not vary widely?	N/A	Yes		N/A	N/A / N/A / Yes		

(Continued)

	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	N/A	Substantial	N/A	N/A / N/A / Substantial
	Was the direction of effect consistent?	N/A	Yes	N/A	N/A / N/A /Yes
	What was the magnitude of statistical heterogeneity (as measured by I ² statistic) - low (I ² < 40%), moderate (I ² 40%-60%), high I ² > 60%)?	N/A	Low	N/A	N/A / N/A / Low
	Was the test for heterogeneity statistically significant (P < 0.1)?	N/A	Not statistically significant	N/A	N/A / N/A /Not statistically significant
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Applicable	Applicable/Applicable/Applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable/Highly applicable/Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes/Yes/Yes
	Was the outcome timeframe sufficient?	Yes	Sufficient	Yes	Yes/Yes/Yes
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes/Yes/Yes

(Continued)

Imprecision^d	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	N/A	Yes	No (↓)	No (↓)/No (↓)/No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: < 100 participants)? ^b	Low (↓)	Low (↓)	Low (↓)	Low (↓)/Low (↓)/Low (↓)
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5-10 studies, small: < 5 studies)? ^b	Small (↓)	Small (↓)	Small (↓)	Small (↓)/Small (↓)/Small (↓)
	Was the outcome a common event (e.g. occurs > 1/100)?	No (↓)	Yes	Yes	Yes/Yes/Yes
Publication bias^e	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes/Yes/Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes/Yes/Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes/Yes/Yes
	There was no industry influence on studies included in the review?	Yes	Yes	Yes	Yes/Yes/Yes
	There was no evidence of funnel plot asymmetry?	N/A	N/A	N/A	N/A / N/A / N/A
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear	Unclear/Unclear/Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bDepends on the context of the systematic review area

^cQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^dWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^eQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of [Summary of findings 2](#); **N/A**: not applicable; **T2DM**: type 2 diabetes mellitus

Appendix 19. Adjustment for high discontinuation rate in acarbose arm of STOP-NIDDM study

Adjustment for high discontinuation rate in acarbose arm of STOP-NIDDM 2002

Outcome	Effect size without correction OR (95% CI)	Effect size with correction OR (95% CI)
Incidence of T2DM	0.67 (0.54 to 0.84)	0.78 (0.63 to 0.97)
Incidence of any cardiovascular disease	0.46 (0.25 to 0.86)	0.52 (0.29 to 0.95)
Incidence of MI	0.08 (0.01 to 0.64)	0.08 (0.01 to 0.64)
Incidence of angina pectoris	0.41 (0.15 to 1.18)	0.50 (0.19 to 1.34)
Incidence of revascularisation procedures	0.55 (0.26 to 1.15)	0.60 (0.29 to 1.23)
Incidence of congestive heart failure	0.20 (0.01 to 4.19)	0.20 (0.01 to 4.19)
Incidence of cerebrovascular events	0.50 (0.09 to 2.75)	0.50 (0.09 to 2.75)
Incidence of peripheral vascular events	1.01 (0.06 to 16.11)	1.01 (0.06 to 16.11)

CI: confidence interval; MI: myocardial infarction; OR: odds ratio; T2DM: type 2 diabetes

WHAT'S NEW

Date	Event	Description
6 December 2018	New citation required and conclusions have changed	This is an update of the Cochrane Review (first published 2006, Issue 4). We have updated the original review from 2006 with five additional trials (evidence up to date as of December 2017).

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

SM: acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates

PL: protocol draft, data interpretation, review of drafts and future review updates

RA: protocol draft, data analysis, data interpretation, review of drafts and future review updates

WG: protocol draft, data analysis, data interpretation, review of drafts and future review updates

FL: protocol draft, acquisition of trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates

DECLARATIONS OF INTEREST

SM: none known

PL: co-author of a trial mentioned in the background and discussion ([Van de Laar 2005](#)).

RA: co-author of a trial mentioned in the background and discussion ([Van de Laar 2005](#)).

WG: none known.

FL: author of a trial mentioned in the background and discussion ([Van de Laar 2005](#)).

SOURCES OF SUPPORT

Internal sources

- Radboud University Nijmegen Medical Centre, Netherlands.

External sources

- WHO, Other.

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NOTES

Portions of the background and methods sections, the appendices, additional tables and figures 1 to 3 of this review are based on a standard template established by Cochrane Metabolic and Endocrine Disorders.

INDEX TERMS

Medical Subject Headings (MeSH)

Acarbose [adverse effects] [*therapeutic use]; Blood Glucose [*drug effects]; Cause of Death; Diabetes Mellitus, Type 2 [epidemiology] [*prevention & control]; Diet; Exercise; Fasting [*blood]; Glucose Intolerance [*drug therapy]; Glycoside Hydrolase Inhibitors [adverse effects] [*therapeutic use]; Incidence; Inositol [adverse effects] [*analogs & derivatives] [therapeutic use]; Metformin [adverse effects] [therapeutic use]; Prediabetic State [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans