DOI: 10.1111/j.1464-5491.2011.03303.x

Article: Treatment

Oral anti-diabetic drugs for the prevention of Type 2 diabetes

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Accepted 17 March 2011

Abstract

Aim To determine the comparative efficacy of oral anti-diabetic drugs in preventing the development of Type 2 diabetes.

Methods A systematic literature search of MEDLINE, EMBASE and Cochrane CENTRAL was conducted for randomized controlled trials evaluating oral anti-diabetic drugs in patients at high risk for developing Type 2 diabetes. Mixed-treatment comparison meta-analysis methods were used to evaluate the relative risks and risk differences of developing Type 2 diabetes, along with associated 95% credible intervals.

Results Overall, 20 trials (n = 23 230 participants) were included. Upon mixed-treatment comparison meta-analysis, thiazolidinediones, alpha-glucosidase inhibitors and biguanides significantly reduced the relative risk of developing diabetes by 64, 40 and 27%, respectively, compared with control. Sulphonylureas and glinides showed no significant effect. Moreover, thiazolidinediones significantly reduced the relative risk of diabetes by 50% compared with biguanides and trended towards a 40% risk reduction vs. alpha-glucosidase inhibitors [relative risk 0.60 (95% credible intervals 0.34–1.02)]. None of the results were appreciably altered upon subgroup or sensitivity analyses. When evaluating risk differences compared with control, thiazolidinediones (−9%, number needed to treat = 11), alpha-glucosidase inhibitors (−7%, number needed to treat = 14) and biguanides (−7%, number needed to treat = 14) continued to show significant benefit.

Conclusions Of the oral anti-diabetic drugs evaluated to prevent Type 2 diabetes, thiazolidinediones were associated with the greatest risk reduction compared with control and associated with greater risk reduction than biguanides. Alpha-glucosidase inhibitors and biguanides performed similarly, and better than control, while sulphonylureas and glinides provided no significant benefit.

Diabet. Med. 28, 948–964 (2011)

Keywords hypoglycaemic drugs, meta-analysis, oral anti-diabetic drugs, prevention, Type 2 diabetes mellitus

Introduction

Type 2 diabetes is a complex illness, which requires intensive management [1]. Treatment prevents some of its complications, but does not usually restore normoglycaemia or eliminate all adverse consequences. Therefore, efforts should be made to prevent diabetes in populations at high risk for developing the disease. Those at high risk include: women who have experienced gestational diabetes; patients with impaired glucose tolerance, impaired fasting glucose or HbA_{1c} 39–46 mmol/mol (5.7–6.4%); or people who are obese [1,2].

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Current guidelines recommend that patients with impaired fasting glucose, impaired glucose tolerance or HbA_{1c} 39–46 mmol/mol (5.7–6.4%) participate in lifestyle modifications, which have shown benefit in decreasing the risk of diabetes development [1]. Additionally, guidelines state that the use of metformin along with lifestyle modifications may be considered in patients at high risk [1]. Other oral anti-diabetic drugs are not currently recommended for diabetes prevention, even although randomized controlled trials [3–6] have demonstrated efficacy compared with control.

While drugs from different oral anti-diabetic drug classes have been studied and found to be useful in the prevention of diabetes, current available data also suggest that there may be important differences in drugs' comparative efficacy. Unfortunately, the nature of the comparisons conducted in clinical trials leads to difficulty in determining the comparative efficacy of these agents

for the prevention or delay of diabetes when using only traditional meta-analytic techniques. Mixed-treatment comparison meta-analysis may be particularly useful in the above cases, allowing for the utilization of both direct and indirect evidence in the determination of endpoints when employing different treatment modalities. We aimed to determine the comparative efficacy of oral anti-diabetic drugs in the prevention of Type 2 diabetes.

Research design and methods

Literature search

Two investigators conducted a literature search for all relevant articles to February 2010 from the earliest possible date of the following sources: MEDLINE (beginning 1950), EMBASE (beginning 1990) and Cochrane CENTRAL (indexed January 2010). We combined terms for different oral anti-diabetic drugs with terms for patients at high risk of developing diabetes. The search strategy is provided in the Supporting Information (Appendix S1). No language restrictions were imposed. A manual search of references from reports of clinical trials and review articles was performed to identify additional relevant studies. Three investigators reviewed all potentially relevant articles independently, with disagreement resolved by discussion.

Study selection

Trials included in the analysis were: randomized and controlled (placebo-treated, untreated control or active control); evaluated at least one of the following oral anti-diabetic drug classes as monotherapy: thiazolidinediones, biguanides, alpha-glucosidase inhibitors, sulphonylureas, glinides or dipeptidyl peptidase-4 inhibitors; enrolled patients at 'high risk' for developing Type 2 diabetes [e.g. impaired glucose tolerance, impaired fasting glucose, HbA_{1c} 39–46 mmol/mol (5.7–6.4%), history of gestational diabetes or obesity] and reported data on the incidence of developing new-onset Type 2 diabetes. Studies were excluded if they solely enrolled patients with polycystic ovary syndrome, cystic fibrosis or who were infected with the human immunodeficiency virus. Studies with < 3 months of treatment duration or which enrolled < 20 participants per treatment group were also excluded. Although lifestyle modification and other commonly used drug classes (e.g. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins and fibrates) are thought to have effects on the development of diabetes, they were not evaluated in this analysis as separate entities because they would likely be highly utilized as background therapies in the target population.

Data abstraction

Through the use of a standardized tool, three investigators independently abstracted data, with disagreements resolved by discussion. The following information was sought from each trial: author identification, year of publication, study design and methodological quality described below, sample size, criteria for study inclusion and for determining 'high-risk' status, a calculation of baseline risk of new-onset Type 2 diabetes (control rate/person-year), duration of patient follow-up (mean and total person-years), drug, dose and schedule utilized, baseline utilization of other medications, use of concurrent lifestyle modification, the number of patients developing new-onset diabetes in each treatment group and the definition of diabetes used (e.g. World Health Organization [7,8], American Diabetes Association [9–11] or non-standard definitions). Quality assessment was performed using the Jadad scale, which assessed randomization, double-blinding and patient withdrawals [12].

Statistical analysis

Traditional meta-analysis was first undertaken, using the incidence of new-onset diabetes as a dichotomous variable. Separate analyses were conducted for all oral anti-diabetic drugs as a group and then for each class of oral anti-diabetic drug separately. In all cases, weighted averages were reported as relative risks with associated 95% confidence intervals, as well as risk differences with associated 95% confidence intervals, using a random-effects model [13]. Statistical heterogeneity was assessed using the I^2 statistic, where values of 25, 50 and 75% represent low, moderate and high degrees of heterogeneity, respectively. Egger's weighted regression statistic *P*-values were used to assess for the presence of publication bias. Traditional meta-analysis of statistics was performed using StatsDirect statistical software, version 2.7.2 (StatsDirect Ltd, Cheshire, UK). A P-value < 0.05 was considered significant for all analyses.

In addition to traditional meta-analysis, we conducted mixed-treatment comparison meta-analysis [14,15]. Mixed-treatment comparison methods were used to compare the different oral anti-diabetic drug classes. These methods are a generalization of meta-analysis methods because they allow comparisons of agents not addressed within any of the individual trials. In addition to analysing the direct within-trial comparisons between two treatments (such as thiazolidinediones vs. placebo), the mixed-treatment comparison framework enabled us to incorporate the indirect comparisons constructed from two trials that have one treatment in common (such as thiazolidinediones vs. placebo and placebo vs. metformin, allowing the indirect comparison of thiazolidinediones to metformin). This type of analysis safeguards the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. All mixed-treatment comparison analyses were conducted using a Bayesian Markov Chain Monte Carlo method and fitted in WinBUGS using a random-effects model. The analyses calculated both the relative risk and the risk difference of developing diabetes for all treatments relative to placebo/control (referent) with associated 95% credible intervals. Residual deviance was calculated for each outcome. A residual deviance which approximates the number of unconstrained datapoints within the model suggests a good fit [14].

The degree of incoherence between results of mixed-treatment comparison and traditional meta-analysis was assessed through qualitatitive comparison of results for each matched drug–drug comparison derived from both meta-analytic methodologies. In the absence of marked differences in effect size, the traditional and mixed-treatment comparison meta-analyses were considered to provide coherent results.

Subgroup analyses were performed, whereby included trials were stratified by various factors and the mixed-treatment comparison relative risks were reanalysed. Because of the unknown effects concurrent lifestyle modification may have on oral anti-diabetic drug efficacy, subgroups included only studies that had either forced lifestyle modification or lifestyle advice, excluding those which had no advice or other lifestyle intervention or, in a separate analysis, excluded studies which specifically had forced lifestyle modifications. Because of the time-dependent development of Type 2 diabetes, we also performed a subgroup analysis excluding trials which were < 1 year in duration, as well as an analysis evaluating trials which were 1–5 years in duration. Additional subgroup analyses were performed evaluating trials for which the control risk per person-year was ≤ 0.09, a value selected because it represents the upper bound of risk for developing diabetes in patients with untreated impaired fasting glucose or impaired glucose tolerance [16].

To assess the effect of methodological heterogeneity on our results, sensitivity analyses were also conducted. As not all included studies enrolled patients using the same definition for 'high risk', we conducted a sensitivity analysis whereby we included only trials which specified definition of impaired glucose tolerance and/or impaired fasting glucose as inclusion parameters. Likewise, the definition of the development of diabetes also varied among the included trials, so a sensitivity analysis was performed excluding trials which used a non-standard definition of diabetes (not utilizing either the World Health Organization or American Diabetes Association definitions). Some of the trials included in the analysis included oral anti-diabetic drugs that are no longer available for use, so an analysis excluding these agents was conducted. Studies of poorer methodological quality may also exhibit inaccurate treatment effects, but including only higher-quality studies may result in increased internal validity at the cost of external validity of the analysis. To reconcile this issue, sensitivity analyses were performed excluding studies with a Jadad score < 3. Additionally, the Diabetes Prevention Program (DPP) trial was published in two ways: the initial publication involved the comparison of placebo, metformin and lifestyle modification [17], but the trial had also originally evaluated troglitazone (discontinued because the drug was withdrawn from the market) and results up to the time point when troglitazone was discontinued were also published [18]. Because the interim analysis included fewer patients than the final analysis, these data were excluded from our base-case analysis. However, to provide additional thiazolidinedione data, in sensitivity analysis, the interim results including thiazolidinedione data were substituted for the final data.

Results

The summary of trial identification and inclusion is provided in Fig. 1. A total of 20 trials (n = 23 230) were included in our meta-analyses [3–6,17–34]. Although trials which evaluated dipeptidyl peptidase-4 inhibitors were eligible for analysis, none were identified and are therefore not evaluated in this meta-analysis. Of note, the Fasting Hyperglycemia Study [35] was excluded because it enrolled subjects with baseline diabetes based on the World Health Organization oral glucose tolerance test.

Tables 1 and 2 summarize the 20 trials included. Definitions of increased diabetes risk varied among elevated BMI, elevated random blood glucose, impaired fasting glucose and impaired glucose tolerance. Definitions of diabetes development also varied, but most trials used criteria set by the World Health Organization [3,23,25,27,30,31,33,34] or the American Diabetes Association [5,6,26,27,34]. Patient follow-up ranged from 0.3 to 7 years (median 2.7 years). Quality assessment using the Jadad scale is also presented.

Upon traditional meta-analysis, the use of any oral anti-diabetic drug statistically significantly reduced the relative risk of developing Type 2 diabetes by 39% compared with placebo/non-active control (Table 3, Fig. 2). Biguanides, thiazolidinediones and alpha-glucosidase inhibitors were associated with decreased relative risk and risk difference of developing diabetes compared with placebo/control upon traditional meta-analysis (Figs 2 and 3). Upon mixed-treatment comparison meta-analysis (Tables 3 and 4, Figs 4 and 5), compared with placebo/control, biguanides (relative risk 0.73; risk difference −0.07), thiazolidinediones (relative risk 0.36; risk difference −0.09) and alpha-glucosidase inhibitors (relative risk 0.60; risk difference −0.07) were associated with significant benefit in the prevention of diabetes. Sulphonylureas and glinides were not associated with alterations in the risk of development of diabetes in either traditional or mixed-treatment comparison meta-analysis. In cases where both traditional and mixed-treatment comparison meta-analysis could be performed, there were no qualitative differences between results, suggesting coherence between methodologies. Good mixed-treatment comparison model fit was suggested by calculated residual deviance similar to the number of unconstrained data points (40 and 42, respectively, for the relative risk evaluation; 25 and 24, respectively, for the risk difference evaluation). In traditional meta-analysis, moderate-to-high degrees of statistical heterogeneity were detected in the analyses of all treatments vs. placebo/control and alpha-glucosidase inhibitors vs. placebo/control, although all studies showed similar direction of effect. A low likelihood for publication bias was expected (P > 0.18 for all).

Discussion

Upon traditional and mixed-treatment comparison meta-analysis, alpha-glucosidase inhibitors, biguanides and thiazolidinediones individually reduced the relative risk of diabetes by 23% to 63%. No benefit was seen with

sulphonylureas or glinides. Our mixed-treatment comparison meta-analysis demonstrated that thiazolidinediones were associated with less risk of diabetes development than biguanides (relative risk 0.49, 95% credible interval 0.28–0.84) and just missed obtaining statistically significant reductions compared with alpha-glucosidase inhibitors (relative risk 0.60, 95% credible interval 0.34–1.02), providing important new data regarding the comparative efficacy of oral anti-diabetic drugs in the prevention of diabetes.

It is hypothesized that thiazolidinediones, alpha-glucosidase inhibitors and biguanides prevent the development of diabetes by preserving pancreatic B-cell function. Thiazolidinediones improve insulin sensitivity and glucose utilization, enabling B-cells to reduce secretion of insulin as well as act upon the B-cell itself [36,37]. Alpha-glucosidase inhibitors reduce carbohydrate digestion and postprandial hyperglycaemia, decreasing the need for B-cells to release greater amounts of insulin to regulate plasma glucose levels [38]. Biguanides suppress endogenous glucose production, thereby reducing fasting plasma glucose concentrations [36]. As sulphonylureas and glinides stimulate the release of insulin from B-cells [36], it is possible that they increase B-cell workload, which ultimately contributes to their future inability to produce sufficient quantities of insulin and their failure to prevent diabetes.

A previous meta-analysis evaluating oral anti-diabetic drugs to prevent diabetes has been published by Gillies and colleagues, and presented a pooled result for all oral anti-diabetic drugs (vs. control) consistent with our own (hazard ratio 0.70, 95% CI 0.62–0.79). It should be noted, however, that this previous meta-analysis only included trials of alpha-glucosidase inhibitors, biguanides and sulphonylureas and thus could not draw conclusions regarding the diabetes prevention efficacy of thiazolidinediones or glinides [39]. Furthermore, the meta-analysis by Gillies *et al.* did not utilize mixed-treatment comparison meta-analysis methods and was consequently unable to assess the comparative efficacy of oral anti-diabetic drugs. Mixed-treatment comparison and other types of network meta-analyses strengthen indirect comparisons between drugs which have either no or insufficient head-to-head trials. These analyses have been conducted in various clinical settings including diabetes, hypertension and atrial fibrillation [40–43].

Current American Diabetes Association guidelines emphasize the use of lifestyle modification to prevent or delay Type 2 diabetes. Metformin is the only pharmacologic treatment recommended for diabetes prevention, and only for those at very high risk (defined as having both impaired glucose tolerance and impaired fasting glucose plus one additional risk

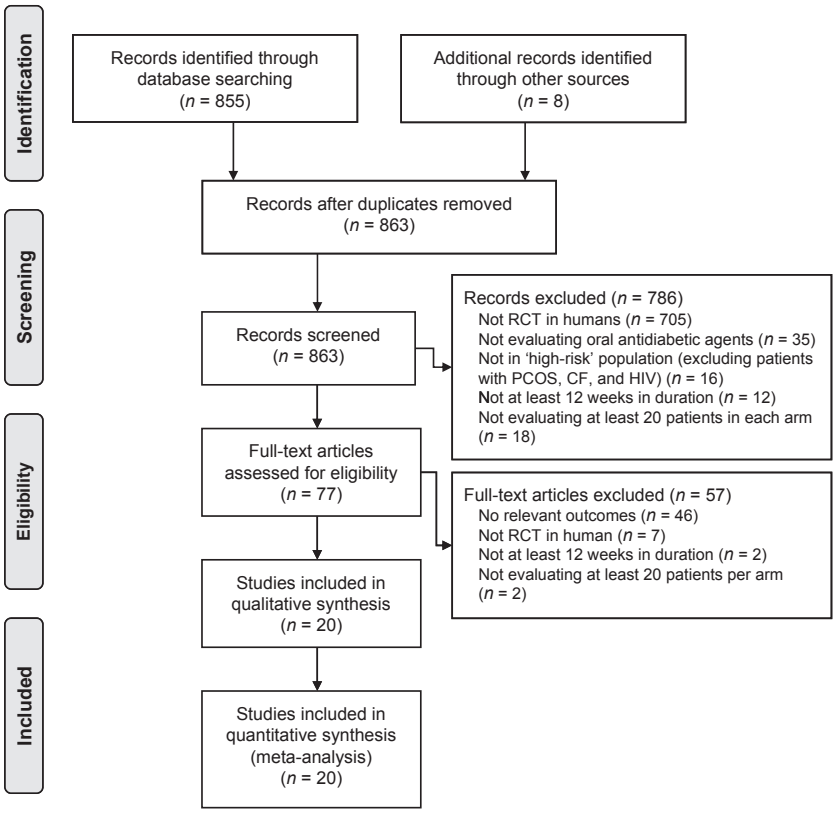

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study indentification, selection, exclusion and inclusion of randomized controlled trials (RCTs) that evaluate the use of oral anti-diabetic drugs in the prevention of Type 2 diabetes. CF, cystic fibrosis; HIV, human immunodeficiency virus; PCOS, polycystic ovary syndrome.

Table 1 Summary of clinical trials of oral anti-diabetic drugs to prevent development of diabetes

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
Keen *et al.*, 1973 *n* = 248	1,1,0 (2)	Age (years): 58;55 Males: 53% BMI: NR Weight (lbs): 150;154	NR	Borderline diabetes: blood glucose 120–199 mg/dl after 50-g OGTT	Two consecutive 2-h PPG > 200 mg/dl; three nonconsecutive 2-h blood glucose > 200 mg/dl; or one 2-h PPG > 200 mg/dl plus 'signs'	Approximately equal subgroups of carbohydrate restricted and 'placebo' diet	Tolbutamide 500 mg twice daily Placebo
Jarrett *et al.*, 1979 *n* = 204	1,2,1 (4)	Age (years): 56.7 Males: 100% BMI (kg/m^2): 26.2	NR	Borderline diabetes, one of the following: (i) Survey blood glucose 110–199 mg/dl and standard 50-g OGTT; (ii) peak blood glucose > 180 mg/dl and 2-h PPG 120–199 mg/dl, and/or mean 2-h PPG > 120 mg/dl	One of the following: (i) two successive 2-h PPG > 200 mg/dl; (ii) three non-successive 2-h PPG > 200 mg/dl; (iii) development of unequivocal symptoms or signs of diabetes; (iv) 50-g OGTT > 200 mg/dl at 10th (last) visit regardless of previous blood glucose	120 g/day carbohydrate diet or 'limit sucrose intake'	Phenformin 50 mg once daily Placebo
Sartor *et al.*, 1980 *n* = 97	0,2,1 (3)	Age (years): 60.2;63.4 Males: 100% BMI (kg/m^2): NR	NR	3-h OGTT with blood glucose levels taken at 10 time points: not falling under definition of diabetes (all values above mean + 3 SD) or normal (all values below mean + 2 SD)	OGTT: all 10 blood glucose values above mean + 3 SD	Diet regulation: limit intake of carbohydrates and lipids and, if overweight, that they should reduce total energy intake	Tolbutamide 500 mg twice daily Placebo
BIGPRO, 1996 *n* = 457	1,2,1 (4)	Age (years): 49.1 Males: 32.7% BMI (kg/m^2): 32.9	NR	High waist–hip ratio: men ≥ 0.95, women ≥ 0.80	Clinical suspicion (weight loss and polyuro-polydipsia); elevated FBG confirmed by subsequent FBG	Diet and exercise advice	Metformin 850 mg twice daily Placebo
Wang *et al.*, 2000 *n* = 60	1,0,0 (1)	Age (years): 64; 63 Males: 53% BMI (kg/m^2): 22.7; 21	NR	IGT according to WHO 1985†	WHO criteria (1985)†	5 h training about diet in treatment and prevention of diabetes	Acarbose 50 mg three times daily Control

Table 1 (*Continued*)

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
Lehtovirta *et al.*, 2001 *n* = 40	1,1,0 (2)	Age (years): 57.3; 58.6 Males: 63% BMI (kg/m^2): 29.8; 30.2	NR	First-degree relative of patients with Type 2 diabetes, BMI 25–35 kg/m^2 and fulfilled WHO criteria for IGT†	NR	NR	Metformin 500 mg twice daily Placebo
Li *et al.*, 2001 *n* = 85	1,1,1 (3)	Age (years): 49; 50 Males: 71% BMI (kg/m^2): NR	NR	IGT after 75-g OGTT per WHO criteria (1985)†	WHO criteria (1985)†	NR	Metformin 250 mg three times daily Placebo
DPP, 2002 *n* = 2155	1,1,0 (2)	Age (years): 50.3; 50.9 Males: 31%; 33.8% BMI (kg/m^2): 34.2; 33.9	NR	BMI ≥ 24 kg/m^2 (≥ 22 in Asians); FBG 95–125 mg/dl; and 75-g OGTT 140–199 mg/dl Prior to 1997, FBG 100–139 mg/dl	ADA criteria (1997)‡	Standard lifestyle: annual 20- to 30-min session to emphasize importance of healthy lifestyle. Encouraged to follow Food Guide Pyramid and the equivalent of NCEP step I diet, to reduce weight and increase physical activity	Metformin 850 mg twice daily Placebo
STOP-NIDDM, 2002 *n* = 1368	2,2,1 (5)	Age (years): 54.3; 54.6 Males: 48%; 50% BMI (kg/m^2): 31; 30.9	NR	BMI 25–40 kg/m^2; 75-g OGTT 7.8–-1.1 mmol/l (140–200 mg/dl); and FBG 5.6–7.7 mmol/l (100–140 mg/dl)	WHO criteria (1985)†	Instructions on weight-reduction or weight-maintenance diet and encouragement to exercise regularly	Acarbose 100 mg three times daily Placebo
TRIPOD, 2002 *n* = 236	1,1,0 (2)	Age (years): 34.9; 34.3 Males: 0% BMI (kg/m^2): 30.6; 30.3	NR	Had GDM in the past 4 years; sum of five OGTT blood glucose levels ≥ 625 mg/dl (34.7 mmol/l)	ADA criteria (1997)‡	Dietary advice given and advised to walk for 30 min 3 days of the week	Troglitazone 400 mg daily Placebo
Pan *et al.* 2003 *n* = 252	2,2,0 (4)	Age (years): 53.4; 55.6 Males: 39.2; 40.9 BMI (kg/m^2): 25.6; 25.8	NR	IGT after 75-g OGTT per WHO criteria (1999)§	ADAssociation criteria (1997)‡	NR	Acarbose 50 mg three times daily Placebo

Table 1 (*Continued*)

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
Fang *et al*., 2004 *n* = 124	2,0,1 (3)	Age (years): 50; 50; 47 Males: 62%; 59%; 63% BMI (kg/m^2): 24.9; 25.2; 24.8	NR	IGT according to WHO 1985†	WHO criteria (1985)†	NR	Acarbose 25–50 mg three times daily Metformin 125–250 mg three times daily Control
Maji *et al*., 2005 *n* = 144	1,0,0 (1)	Age (years): NR Males: NR BMI (kg/m^2): NR Authors reported mean for all study groups; for our MTC, we did not include data for intensive lifestyle modification	NR	FBG < 110 mg/dl and 75-g OGTT 110–200 mg/dl	NR	'Appropriate' diet by registered dietitian of endocrine clinic of the institute and regular exercise schedule	Metformin 500 mg daily Rosiglitazone 2 mg daily Acarbose 25 mg daily
DREAM, 2006 *n* = 5269	2,2,1 (5)	Age (years): 54.6; 54.8 Males: 41.7%; 39.9% BMI (kg/m^2): 30.8; 31.0	%—I;C asprin or anti-platelet: 14.4;14.3 Thiazide diuretics: 9.3; 10.1 Other diuretic or aldosterone antagonist: 6; 5.5 ARB: 5.8; 5.1 β-blocker: 17.8; 16.8 Statin or fibrate: 14.8; 14.8	One of the following: (i) IFG [FBG 6.1–7 mmol/l (110–126 mg/dl) and 75-g OGTT ≤ 11.1 mmol/l (200 mg/dl)]; (ii) IGT [FBG < 7 mmol/l (< 126 mg/dl) and 75-g OGTT 7.8–11.1 mmol/l (140–200 mg/dl)]; (iii) In 2003, added isolated IFG [FBG 6.1–7 mmol/l (110–126 mg/dl) and 75-g OGTT < 7.8 mmol/l (140 mg/dl)]	WHO criteria (1999) or ADA criteria (2003)	At all visits, importance of healthy diet and lifestyle was emphasized	Rosiglitazone 8 mg daily Placebo

Table 1 (*Continued*)

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
IDPP-1 2006 n = 502	1,0,1 (2)	Age (years): 45.9 Males: 79% BMI (kg/m^2): 25.8	NR	IGT according to WHO Criteria on two occasions§	WHO criteria (1999)	All patients: depending on baseline physical activity, advised to continue as normal or to walk briskly ≥ 30 min/day Standard healthcare advice: above only Lifestyle modification: reduction in total calories, refined carbohydrates and fats, avoidance of sugar and inclusion of fibre-rich foods	Metformin 500 mg twice daily Control
PPAR 2007 n = 200	1,1,0 (2)	Age (years): 59.4; 59.4 Males: 80.4%; 79.6% BMI (kg/m^2): NR	Asprin: 80.4; 82.7 β-blocker: 82.4; 78.6 Anti-inflammatory: 24.5; 21.4 ACE inhibitor/ARB: 51; 46.9 Lipid-lowering: 79.4; 83.7 Thienopyridine: 44.1; 38.8 Diuretic: 17.6; 11.2	Undergoing PCI with angiographic evidence of CAD, obese (BMI > 27 kg/m^2 or waist circumference > 40 inches in males and > 35 inches in females plus one of the following: (i) hypertension, (ii) dyslipidaemia, (iii) treated hyperlipidaemia, or (iv) HbA_{1c} > 6.0% or FBG ≥ 110 mg/dl (excluding patients who required pharmacologic treatment for diabetes)	NR	NR	Rosiglitazone 4 mg twice daily Placebo
DAISI, 2008 *n* = 118	2,2,1 (5)	Age (years): 58.5; 56.5 Males: 50.8%; 51% BMI (kg/m^2): 28.4; 29.5	NR	Mean FBG < 7.8 mmol/l, mean 2-h PPG 8.6–11.1 mmol/l and HbA_{1c} ≤ 7.0%	WHO criteria (1985)†	NR	Acarbose 50 mg three times daily Placebo

Table 1 (*Continued*)

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
Kawamori *et al.*, 2009 *n* = 1778	2,2,1 (5)	Age (years): 55.7; 55.7 Males: 60%; 60% BMI (kg/m^2): 25.76; 25.89	NR	FBG < 6.9 mmol/l, 2-h PPG 7.8–11 mmol/l, HbA_{1c} < 6.5% plus one of the following: (i) high normal blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or being treated for hypertension; (ii) dyslipidaemia (total cholesterol ≥ 5.7 mmol/l, triglyceride ≥ 1.7 mmol/l or HDL < 1.04 mmol/l); (iii) obesity (BMI ≥ 25 kg/m^2); or (iv) family history of diabetes	WHO criteria (1999)	All patients given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualized guidance on future lifestyle habits based on intensity of daily activity categories defined by the Japanese Ministry of Health and Labour)	Voglibose 0.2 mg three times daily Placebo
ACT NOW, 2009 *n* = 602	2,2,1 (5)	Age (years): 52.3 Males: 42% BMI (kg/m^2): 34.3	Pending publication	Impaired glucose tolerance: FBG ≥ 95 mg/dl and at least one other high-risk characteristic	ADA criteria (2003)	All patients given 30-min of instruction by a dietician with goals emphasizing reduced caloric intake, decreased fat intake and walking 30 min per day for 4–5 days per week	Pioglitazone 45 mg daily Placebo

Table 1 (*Continued*)

Study¶	Jadad score*	Population characteristics (mean) I;C	Concurrent medications	Inclusion parameters pertaining to diabetes risk	Definition of diabetes development	Concurrent diet	Interventions evaluated
NAVIGATOR, 2010 *n* = 9306	2,1,1 (4)	Age (years): 63.7; 63.8 Males: 49%; 49.7% BMI (kg/m^2): 30.5; 30.5 Weight (lbs): 183.9; 183.9	ASA or other antiplatelet: 36.9; 36.8 ACE inhibitor: 7.1; 7.4 ARB: 0.3; 0.4 BB: 40.3; 38.5 CCB: 32.7; 32.0 Diuretic: 31.5; 32.2 Lipid-lowering: 38.7; 38.2	Impaired glucose tolerance, fasting plasma glucose ≥ 95 mg/dl and ≤ 126 mg/dl, and one or more cardiovascular risk factors (if older than 55 years of age) or known cardiovascular disease (if older than 50 years of age)	ADA criteria (1997) or WHO criteria (1998)	Lifestyle intervention aimed to reduce risk of diabetes, including achieving and maintaining 5% weight loss, reducing the amount of saturated and total fats in diets and increasing physical activity to 150 min weekly	Nateglinide 60 mg before meals three times daily Placebo

*Jadad Score presented as subscores for randomization (up to 2 points), double-blinding (up to 2 points), description of withdrawals (up to 1 point) and (overall score).

†WHO criteria 1985—normal: not defined; diabetes mellitus: FBG ≥ 7.8 mmol/l (≥ 140 mg/dl) or OGTT ≥ 11.1 mmol/l (≥ 200 mg/dl); IGT: FBG < 7.8 mmol/l (< 140 mg/dl) and OGTT 7.8–11.1 mmol/l (140–200 mg/dl); IFG: not defined [7].

‡ADA criteria 1997—one of the following: (i) symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/l (≥ 200 mg/dl); (ii) FBG ≥ 7.0 mmol/l (≥ 126 mg/dl); or (iii) 75-g OGTT ≥ 11.1 mmol/l (≥ 200 mg/dl) [9].

§WHO criteria 1999—normal: FBG< 6.1 mmol/l (< 110 mg/dl); diabetes mellitus: FBG ≥ 7.0 mmol/l (≥ 126 mg/dl) or OGTT ≥ 11.1 mmol/l (≥ 200 mg/dl); IGT: FBG < 7.0 mmol/l (< 126 mg/dl) and OGTT 7.8–11.1 mmol/l (140–200 mg/dl); IFG: FBG 6.1–7.0 mmol/l (110–126 mg/dl) and OGTT < 7.8 mmol/l (< 140 mg/dl) [8].

¶Study abbreviations: BIGPRO, BIGuanides and Prevention of the Risks in Obesity trial; DPP, Diabetes Prevention Program; STOP-NIDDM, Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus trial; TRIPOD, Troglitazone in Prevention of Diabetes study; DREAM, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication trial; IDPP, Indian Diabetes Prevention Programme; PPAR, Peroxisome proliferators-activated receptor γ agonists for the Prevention of Adverse events following percutaneous coronary Revascularization; DAISI, Dutch Acarbose Intervention Study in persons with Impaired glucose tolerance; ACT NOW, ACTos NOW for the Prevention of Diabetes; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.

ACE, angiotensin converting enzyme; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; C, control; CAD, coronary artery disease; CCB, calcium channel blocker; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; I, intervention; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MTC, mixed-treatment comparison; OGTT, oral glucose tolerance test; NCEP, National Cholesterol Education Program; NR, not reported; PCI, percutaneous coronary intervention; PPG, postprandial glucose; WHO, World Health Organization.

factor: HbA_{1c} > 6%, hypertension, dyslipidaemia or a first-degree relative with diabetes) [1]. These recommendations are based in part on the results of the Diabetes Prevention Program, which suggested that only seven 'high-risk' patients need to be treated with extensive lifestyle modification and 14 treated with metformin over a mean of 2.8 years to prevent one case of progression to diabetes [17]. The corresponding numbers needed to treat from our meta-analysis were 11 for thiazolidinediones and 14 for alpha-glucosidase inhibitors and biguanides (vs. placebo/non-active control) over a median of 2.7 years, suggesting that there may be sufficient evidence to consider using other oral anti-diabetic drug classes, as well as treating patients with a less rigorous definition of 'high risk'.

Table 2 Summary of results of clinical trials of oral anti-diabetic drugs* to prevent development of diabetes

Study†	Duration (years)	Person-years	Control rate per person-year	Drug 1	New cases diabetes mellitus/*n*	Drug 2	New cases diabetes mellitus/*n*	Drug 3	New cases diabetes/*n*
Keen *et al.*, 1973 *n* = 248	7	1736	0.02	SU	13/123	Placebo	11/125	…	…
Jarrett *et al.*, 1979 *n* = 204	5	905	0.03	BI	13/92	Placebo	14/89	…	…
Sartor *et al.*, 1980 *n* = 97	10	970	0.01	SU	5/49	Placebo	6/48	…	…
BIGPRO, 1996 *n* = 457	1	457	0.02	BI	0/227	Placebo	5/230	…	…
Wang *et al.*, 2000 *n* = 60	1	60	0.10	AGI	1/30	Control	3/30	…	…
Lehtovirta *et al.*, 2001 *n* = 40	0.5	20	0.10	BI	1/20	Placebo	1/20	…	…
Li *et al.*, 2001 *n* = 70	1	85	0.14	BI	3/42	Placebo	6/43	…	…
DPP 2002 *n* = 2155	2.8	6034	0.10	BI	233/1073	Placebo	313/1082	…	…
STOP-NIDDM 2002 *n* = 1368	3.3	4514	0.13	AGI	221/682	Placebo	285/686	…	…
TRIPOD 2002 *n* = 236	2.5	590	0.05	TZD	6/114	Placebo	15/122	…	…
Pan *et al.*, 2003 *n* = 252	0.3	75.6	0.31	AGI	7/125	Placebo	12/127	…	…
Fang *et al.*, 2004 *n* = 124	5	620	0.09	AGI	6/45	BI	9/44	Control	15/35
Maji *et al.*, 2005 *n* = 144	3	432	0.00	BI	0/48	TZD	0/48	AGI	0/48
DREAM 2006 *n* = 5269	3	15 807	0.08	TZD	280/2635	Placebo	653/2634	…	…
IDPP-1 2006 *n* = 502	2.5	12575	0.19	BI	100/249	Placebo	120/253	…	…
PPAR 2007 *n* = 200	1	200	0.03	TZD	0/102	Placebo	3/98	…	…
DAISI 2008 *n* = 118	3.1	366	0.08	AGI	11/60	Placebo	14/58	…	…
Kawamori *et al.*, 2009 *n* = 1778	0.92	1636	0.13	AGI	50/897	Placebo	106/881	…	…
ACT NOW 2009 *n* = 602	2.6	1565	0.06	TZD	10/303	Placebo	45/299	…	…
NAVIGATOR 2010 *n* = 9306	5	46 530	7.28E-6	Glinide	1674/4645	Placebo	1580/4661	…	…

*Drugs: AGI, alpha-glucosidase inhibitor; BI, biguanide; SU, sulphonylurea; TZD, thiozolinedione.
†Study abbreviations: BIGPRO, BIGuanides and Prevention of the Risks in Obesity trial; DPP, Diabetes Prevention Program; STOP-NIDDM, Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus trial; TRIPOD, Troglitazone in Prevention of Diabetes study; DREAM, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication trial; IDPP, Indian Diabetes Prevention Programme; PPAR, Peroxisome proliferators-activated receptor γ agonists for the Prevention of Adverse events following percutaneous coronary Revascularization; DAISI, Dutch Acarbose Intervention Study in persons with Impaired glucose tolerance; ACT NOW, ACTos NOW for the Prevention of Diabetes; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.

Table 3 Results of traditional and mixed-treatment comparison meta-analyses of relative risk and risk difference on development of Type 2 diabetes

Comparison	Number of studies in traditional analysis	Traditional relative risk (95% CI)	Mixed-treatment comparison relative risk (95% CrI)	Estimated number needed to treat*	Risk difference (95% CI)	Mixed-treatment comparison risk difference (95% CrI)	Number needed to treat†
All treatments vs. placebo	19	0.61 (0.48–0.77)‡	NA	NA	−0.06 (−0.09 to −0.03)‡	NA	NA
All treatments (minus SU and glinide) vs. placebo	17	0.56 (0.44–0.70)‡	NA	NA	−0.07 (−0.10 to −0.04)‡	NA	NA
Biguanide vs. placebo	7	0.77 (0.69–0.86)	0.73 (0.49–0.98)	37–74	−0.05 (−0.10 to −0.003)§	−0.07 (−0.09 to −0.04)	14
TZDs vs. placebo	4	0.37 (0.25–0.53)	0.36 (0.21–0.52)	16–31	−0.09 (−0.15 to −0.03)†	−0.09 (−0.12 to −0.06)	11
SU vs. placebo	2	1.06 (0.57–2.00)	1.04 (0.49–2.29)	NA	0.007 (−0.06 to 0.07)	0.01 (−0.06 to 0.07)	NA
AGI vs. placebo	6	0.58 (0.41–0.82)§	0.60 (0.40–0.81)	20–39	−0.07 (−0.11 to −0.04)	−0.07 (−0.10 to −0.05)	14
Glinide vs. placebo	1	1.05 (0.99–1.11)	1.06 (0.58–1.96)	NA	0.02 (−0.01 to 0.03)	0.02 (−0.03 to 0.06)	NA
TZDs vs. biguanide	1	1.00 (0.06–17.15)	0.49 (0.28–0.84)	20–39	0.00 (−0.07 to 0.07)	−0.02 (−0.06 to 0.01)	NA
SU vs. biguanide	0	NA	1.44 (0.64–3.53)	NA	NA	0.07 (−8.18E-5 to 0.15)	NA
AGI vs. biguanide	2	0.67 (0.27–1.67)	0.82 (0.52–1.33)	NA	−0.03 (−0.16 to 0.11)	−0.01 (−0.04 to 0.02)	NA
Glinide vs. biguanide	0	NA	1.46 (0.77–3.15)	NA	NA	0.08 (0.03–0.13)	13¶
SU vs. TZDs	0	NA	2.93 (1.29–7.54)	15–30¶	NA	0.09 (0.02–0.17)	13¶
AGI vs. TZDs	1	1.00 (0.06–17.15)	1.67 (0.98–2.97)	NA	0.00 (−0.07 to 0.07)	0.01 (−0.02 to 0.04)	NA
Glinide vs. TZDs	0	NA	2.96 (1.51–6.87)	15–30¶	NA	0.10 (0.05–0.15)	10¶
AGI vs. SU	0	NA	0.57 (0.24–1.26)	NA	NA	−0.08 (−0.15 to −0.01)	13
Glinide vs. SU	0	NA	1.02 (0.38–2.65)	NA	NA	0.01 (−0.07 to 0.09)	NA
Glinide vs. AGI	0	NA	1.77 (0.93–3.78)	NA	NA	0.09 (0.04–0.16)	11¶

*Number needed to treat (NNT) estimated from relative risk (RR) based on a baseline risk of 5–10% of developing Type 2 diabetes, using the formula NNT = 1/[baseline risk × (1 − RR)].
†NNT calculated from pooled risk difference (RD), using formula NNT = 1/RD.
‡$I^2 \geq 75\%$.
§I^2 50–75%.
¶Number needed to harm.
AGI, alpha-glucosidase inhibitor; CI, confidence interval; CrI, credible interval; NA, not applicable; SU, sulphonylurea; TZD, thiozolinedione.

Table 4 Subgroup and sensitivity analysis results on relative risk of developing Type 2 diabetes

Comparison	Base case relative risk (95% CrI)	Concurrent lifestyle modifications or advice (95% CrI)	Excluding trials with forced lifestyle modification (95% CrI)	Trial duration at least 1 year (95% CrI)	Trial duration 1–5 years (95% CrI)	Control risk per person-year ≤ 0.09 (95% CrI)	Inclusion criteria specified IGT or IFG (95% CrI)	Diagnosis by ADA or WHO criteria (95% CrI)	Excluding trials evaluating withdrawn products (95% CrI)	Excluding trials with Jadad score < 3 (95% CrI)	Replacing main DPP data with DPP-troglitazone (95% CrI)
Number of trials in analysis	20	12	18	17	15	12	17	13	18	13	20
Biguanide vs. placebo	0.73 (0.49–0.98)	0.85 (0.20–1.97)	0.65 (0.41–0.90)	0.73 (0.44–0.97)	0.73 (0.42–0.97)	0.53 (0.13–1.20)	0.76 (0.52–1.04)	0.74 (0.47–1.04)	0.69 (0.41–0.98)	0.64 (0.34–0.99)	0.67 (0.44–0.94)
TZDs vs. placebo	0.36 (0.21–0.52)	0.35 (0.13–0.90)	0.36 (0.20–0.53)	0.36 (0.17–0.53)	0.37 (0.16–0.54)	0.33 (0.11–0.66)	0.36 (0.20–0.55)	0.37 (0.22–0.56)	0.34 (0.17–0.54)	0.35 (0.17–0.62)	0.34 (0.21–0.49)
SU vs. placebo	1.04 (0.49–2.29)	0.81 (0.11–5.43)	0.81 (0.20–2.94)	1.04 (0.47–2.32)	ND	1.04 (0.30–3.42)	1.07 (0.49–2.29)	ND	1.05 (0.46–2.39)	0.82 (0.19–3.38)	1.05 (0.47–2.27)
AGI vs. placebo	0.60 (0.40–0.81)	0.59 (0.18–1.47)	0.59 (0.39–0.81)	0.68 (0.34–0.96)	0.68 (0.35–0.98)	0.50 (0.14–1.52)	0.60 (0.41–0.81)	0.60 (0.39–0.82)	0.59 (0.38–0.83)	0.59 (0.36–0.89)	0.59 (0.39–0.81)
Glinide vs. placebo	1.06 (0.58–1.96)	1.07 (0.21–5.37)	ND	1.07 (0.52–2.16)	1.06 (0.50–2.28)	1.06 (0.24–4.75)	1.06 (0.58–1.93)	1.06 (0.55–2.04)	1.06 (0.51–2.22)	1.06 (0.46–2.47)	1.06 (0.57–2.00)
TZDs vs. biguanide	0.49 (0.28–0.84)	0.42 (0.12–3.40)	0.55 (0.30–0.99)	0.50 (0.24–0.90)	0.51 (0.23–0.93)	0.62 (0.18–2.69)	0.48 (0.25–0.83)	0.50 (0.37–0.91)	0.49 (0.24–0.97)	0.54 (0.24–1.28)	0.50 (0.29–0.86)
SU vs. biguanide	1.44 (0.64–3.53)	0.97 (0.13–11.54)	1.26 (0.30–5.04)	1.44 (0.63–3.78)	ND	1.98 (0.48–12.81)	1.42 (0.62–3.28)	ND	1.53 (0.63–4.16)	1.29 (0.28–6.13)	1.57 (0.67–3.82)
AGI vs. biguanide	0.82 (0.52–1.33)	0.69 (0.18–3.81)	0.92 (0.56–1.56)	0.93 (0.50–1.60)	0.94 (0.49–1.71)	0.94 (0.25–5.73)	0.80 (0.48–1.25)	0.81 (0.48–1.36)	0.85 (0.50–1.58)	0.92 (0.50–1.91)	0.87 (0.53–1.46)
Glinide vs. biguanide	1.46 (0.77–3.15)	1.24 (0.24–12.39)	ND	1.43 (0.73–3.67)	1.43 (0.71–3.99)	1.99 (0.43–17.5)	1.40 (0.73–2.89)	1.44 (0.71–3.27)	1.53 (0.73–4.03)	1.64 (0.68–4.98)	1.58 (0.80–3.50)
SU vs. TZDs	2.93 (1.29–7.54)	2.30 (0.26–20.41)	2.20 (0.53–9.59)	2.92 (1.23–8.61)	ND	3.16 (0.82–16.79)	2.98 (1.24–7.67)	ND	3.12 (1.24–9.24)	2.37 (0.48–11.76)	3.12 (1.31–7.78)
AGI vs. TZDs	1.67 (0.98–2.97)	1.66 (0.36–6.44)	1.65 (0.95–3.08)	1.87 (0.94–3.84)	1.87 (0.92–4.17)	1.49 (0.41–7.54)	1.66 (0.93–3.11)	1.62 (0.91–2.92)	1.73 (0.93–3.66)	1.69 (0.79–3.86)	1.73 (1.03–3.02)*
Glinide vs. TZDs	2.96 (1.51–6.87)	2.99 (0.48–20.94)	ND	2.89 (1.42–8.61)	2.84 (1.38–9.43)	3.12 (0.71–23.03)	2.91 (1.47–6.99)	2.87 (1.37–6.91)	3.10 (1.39–9.04)	3.02 (1.13–9.54)	3.13 (1.58–7.14)
AGI vs. SU	0.57 (0.24–1.26)	0.72 (0.08–6.15)	0.76 (0.19–3.04)	0.64 (0.23–1.51)	ND	0.47 (0.09–2.52)	0.56 (0.24–1.28)	ND	0.56 (0.22–1.36)	0.72 (0.16–3.33)	0.56 (0.23–1.31)
Glinide vs. SU	1.02 (0.38–2.65)	1.32 (0.11–17.1)	ND	1.03 (0.36–2.91)	ND	1.02 (0.16–7.04)	0.99 (0.39–2.66)	ND	1.01 (0.34–3.05)	1.30 (0.25–7.06)	1.02 (0.38–2.79)
Glinide vs. AGI	1.77 (0.93–3.78)	1.79 (0.30–14.12)	ND	1.54 (0.79–4.30)	1.53 (0.74–4.60)	2.14 (0.34–14.84)	1.75 (0.34–3.72)	1.77 (0.90–3.98)	1.79 (0.84–4.40)	1.78 (0.72–4.89)	1.81 (0.92–3.94)

*Statistically significant result upon sensitivity analysis.

ADA, American Diabetes Assocation; AGI, alpha-glucosidase inhibitor; CrI, credible interval; DPP, Diabetes Prevention Program; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ND, no data; SU, sulphonylurea; TZD, thiozolinedione; WHO, World Health Organization.

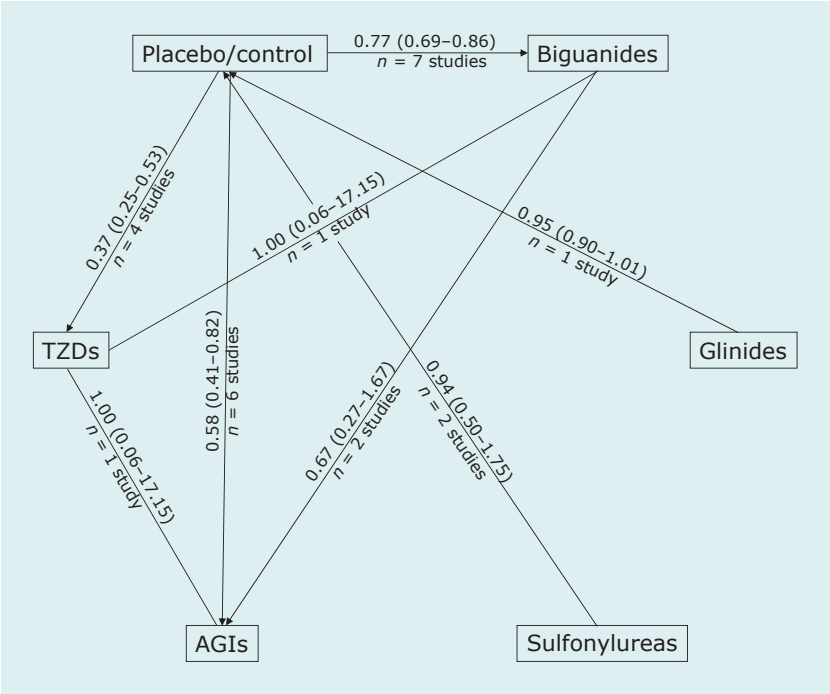

FIGURE 2 Network of results for relative risk of individually run traditional meta-analyses for each pairwise comparison. Arrows are pointing to the class of medications with the lower risk of developing new-onset diabetes. Results are reported as relative risks with 95% confidence intervals referent to the arrow origin. AGIs, alpha-glucosidase inhibitors; TZDs, thiazolidinediones.

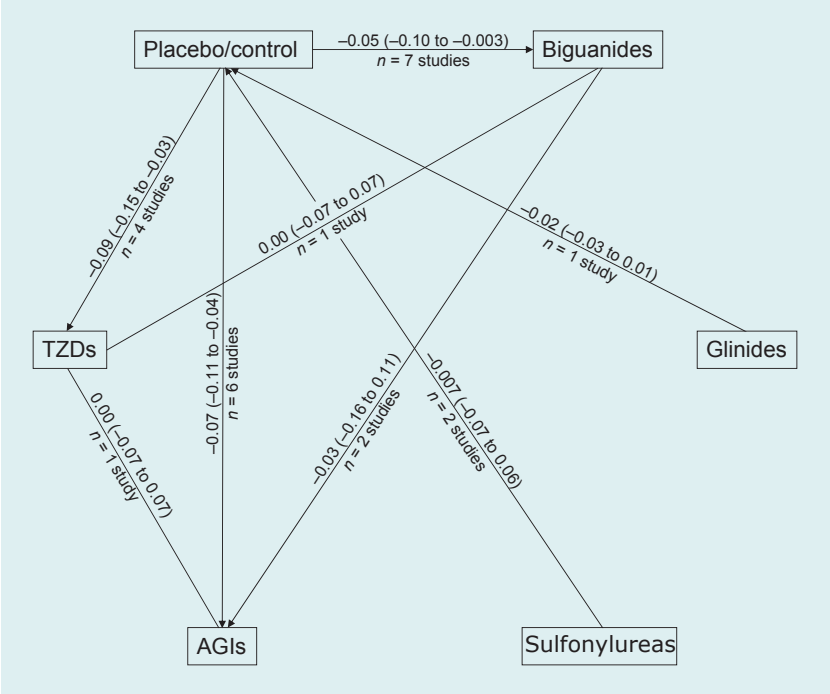

FIGURE 3 Network of results for risk difference of individually run traditional meta-analyses for each pairwise comparison. Arrows are pointing to the class of medications with the lower risk of developing new-onset diabetes. Results are reported as risk differences with 95% confidence intervals referent to the arrow origin. AGIs, alpha-glucosidase inhibitors; TZDs, thiazolidinediones.

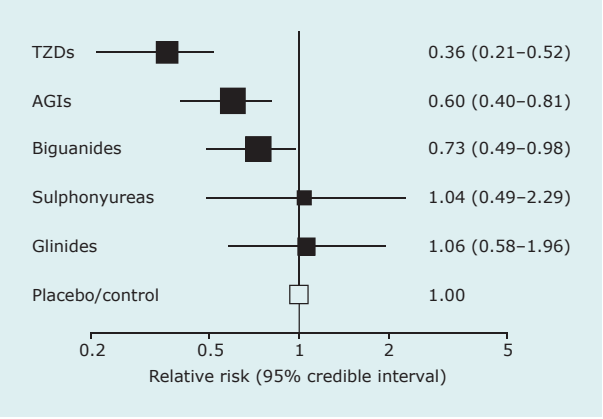

FIGURE 4 Results of the mixed-treatment comparison meta-analysis of trials evaluating the relative risk of oral anti-diabetic drugs to prevent development of new-onset Type 2 diabetes. Size of squares (representing the point estimate for each class of agent) is proportional to the number of patients who developed diabetes. Horizontal lines indicate 95% confidence intervals. Relative risks to the left of the vertical line at unity denote a protective effect compared with placebo or control. AGIs, alpha-glucosidase inhibitors; TZDs, thiazolidinediones.

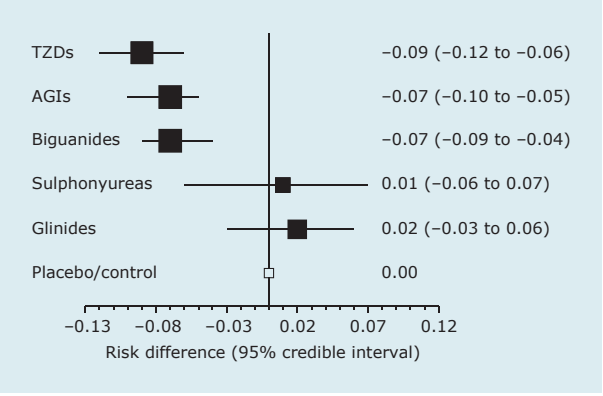

FIGURE 5 Results of the mixed-treatment comparison meta-analysis of trials evaluating the risk difference of oral anti-diabetic drugs to prevent development of new-onset Type 2 diabetes. Size of squares (representing the point estimate for each class of agent) is proportional to the number of patients who developed diabetes. Horizontal lines indicate 95% confidence intervals. Risk differences to the left of the vertical line at unity denote a protective effect compared with placebo or control. AGIs, alpha-glucosidase inhibitors; TZDs, thiazolidinediones.

In addition to efficacy in preventing diabetes, other oral anti-diabetic drug selection considerations include contraindications, adverse events and/or other therapeutic benefits. We were unable to quantify the effect of each oral anti-diabetic drug class on adverse events because of inconsistent reporting. Although thiazolidinediones were found to be most effective, they are not without adverse effects. Of the trials which reported it, patients taking thiazolidinediones gained up to 3.1 kg more in body weight than those taking placebo [3,6]. In one trial, patients with existing angina or heart failure did not experience changes in severity, but 1.2% of rosiglitazone-treated patients experienced new-onset heart failure vs. none of the placebo-treated patients [31]. These data are concerning because of the increased risk of cardiac events with rosglitazone [44,45] and the recent US Food and Drug Administration recommendation for the limited use of rosiglitazone [46]. Fracture rates were not reported in the trials, but there is concern that thiazolidinedione use is associated with increased risk of fracture [47]. Alpha-glucosidase inhibitors more frequently caused gastrointestinal symptoms than placebo, most often flatulence, abdominal pain and diarrhoea, but these events were mild to moderate [4,27,32,33]. Because of the gastrointestinal distress and frequent dosing schedule, patients tend to be non-adherent to alpha-glucosidase inhibitors [48]. In trials evaluating biguanides, the most commonly reported adverse effects were gastrointestinal (diarrhoea, nausea and vomiting) [17,22], but these can be mitigated by titrating up to the optimal dose over several weeks [48]. Metformin is contraindicated in patients with renal disease or renal dysfunction [serum creatinine> 133 μmol/l (1.5 mg/dl) in men or > 124 μmol/l (1.4 mg/dl) in women] and in patients with any acute or chronic metabolic acidosis because of the risk of developing lactic acidosis, but its true lactic acidosis risk has come into question [49].

Some researchers have suggested that the efficacy of oral anti-diabetic drugs in preventing diabetes is a result of their ability to mask disease diagnosis [50]. This theory is supported by the results of the Diabetes Prevention Program and the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM). One to 2 weeks after withdrawal from the Diabetes Prevention Program, more metformin-treated patients developed diabetes than placebo-treated patients (odds ratio 1.49, 95% CI 0.93–2.38) [51]. Similarly, in the STOP-NIDDM trial, more acarbose-treated patients developed diabetes than placebo-treated patients (15 vs. 11%) in the 3 months following withdrawal [4]. However, not all trials of oral anti-diabetic drugs provide data to support 'diagnosis masking' as the mechanism of action. In the Troglitazone in Prevention of Diabetes (TRIPOD) study, the rate of diabetes development in the 8 months following study withdrawal was less in the troglitazone group (2.3 vs. 15% in the placebo group), suggesting a potential protective effect on disease progression [26,37], although this is not supported by the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study [3].

Our mixed-treatment comparison meta-analysis has limitations that should be noted. First, although troglitazone and phenformin are not available in the USA as a result of safety concerns, they were included in this meta-analysis because we felt they added valuable insight into the efficacy of their respective drug classes and increased statistical power when comparing oral anti-diabetic drug classes. However, we did provide results of a sensitivity analysis excluding these drugs and the comparative efficacy of the oral anti-diabetic drug classes remained consistent with our base-case results. Secondly, our systematic review only indentified eligible trials utilizing first-generation sulphonylureas. While not eligible for inclusion in our meta-analysis because of its small sample size, Eriksson *et al.* evaluated

glipizide (a second-generation sulphonylurea) in 37 patients with impaired glucose tolerance and found that, after 6 months of treatment, zero glipizide-treated patients and one patient in the placebo group developed diabetes [52]. Therefore, there is insufficient evidence to definitively refute the efficacy of sulphonylureas in the prevention of diabetes. Next, some of the trials included in our meta-analysis utilized concurrent lifestyle modification in addition to oral anti-diabetic drugs or placebo. While this theoretically could impact our results, upon sensitivity analysis limited to trials including lifestyle modification or advice, we found similar results to our base case, suggesting that lifestyle modifications alone may not be sufficient and that oral anti-diabetic drugs may provide additional benefits. Finally, our meta-analysis did not evaluate dipeptidyl peptidase-4 inhibitors or combinations of agents because of a paucity of published trial data. The recently published Canadian Normoglycaemia Outcomes Evaluation (CANOE) trial suggests that low-dose combination therapy of rosiglitazone plus metformin is also effective in the prevention of Type 2 diabetes [53], but future research may be needed to compare the effects of combination therapy and monotherapy.

Competing interests

Funding for this study was provided by Takeda Pharmaceuticals North America Inc. BES is employed by Takeda Pharmaceuticals North America Inc. There are no other competing interests to disclose.

Acknowledgements

Funding for this study was provided by Takeda Pharmaceuticals North America Inc. OJP and CIC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. MEDLINE search strategy.

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