Effect of Antihyperglycemic Agents Added to Metformin and a Sulfonylurea on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis

Jorge L. Gross, MD, PhD; Caroline K. Kramer, MD, PhD; Cristiane B. Leitão, MD, PhD; Neil Hawkins; Luciana V. Viana, MD, PhD; Beatriz D. Schaan, MD, PhD; Lana C. Pinto, MD; Ticiana C. Rodrigues, MD, PhD; and Mirela J. Azevedo, MD, PhD, for the Diabetes and Endocrinology Meta-analysis Group (DEMA)*

Background: Few studies have examined the effect of adding a third antihyperglycemic drug when blood glucose control is not achieved by using metformin and a sulfonylurea.

Purpose: To compare the efficacy of add-on antihyperglycemic drugs in patients with type 2 diabetes that is not controlled with metformin and a sulfonylurea.

Data Sources: MEDLINE, EMBASE, Cochrane Library, LILACS, and ClinicalTrials.gov electronic databases.

Study Selection: Randomized trials at least 24 weeks in duration. Studies evaluated the effects of adding a third antihyperglycemic drug to treatment of adults aged 18 years or older with type 2 diabetes and a hemoglobin A_{1c} (HbA_{1c}) level greater than 7.0% who were already receiving a combination of metformin and a sulfonylurea.

Data Extraction: Primary end points were change in HbA_{1c} level, change in weight, and frequency of severe hypoglycemia.

Data Synthesis: Eighteen trials involving 4535 participants that lasted a mean of 31.3 weeks (24 to 52 weeks) were included. Compared with placebo, drug classes did not differ in effect on HbA_{1c} level (reduction ranging from −0.70% [95% credible interval {CrI}, −1.33% to −0.08%] for acarbose to −1.08% [CrI, −1.41% to −0.77%] for insulin). Weight increase was seen with insulins (2.84 kg [CrI, 1.76 to 3.90 kg]) and thiazolidinediones (4.25 kg [CrI, 2.76 to 5.66 kg]), and weight loss was seen with glucagon-like peptide-1 agonists (−1.63 kg [CrI, −2.71 to −0.60 kg]). Insulins caused twice the absolute number of severe hypoglycemic episodes than noninsulin antihyperglycemic agents.

Limitations: Most of the trials were short term, and trial quality varied. With so few trials relative to antihyperglycemic agents, investigators relied on indirect comparisons, which increased the uncertainty of the findings and conclusions.

Conclusion: There is no clear difference in benefit between drug classes when adding a third agent to treatment of patients with type 2 diabetes who are already receiving metformin and a sulfonylurea. The most appropriate option should depend on each patient's clinical characteristics.

Primary Funding Source: Conselho Nacional de Desenvolvimento Científico e Tecnológico and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Ann Intern Med. 2011;154:672-679. www.annals.org

For author affiliations, see end of text.

* Group members are listed in **Appendix 1** (available at www.annals.org).

There is consensus that lifestyle changes and metformin should be first-line treatment of patients with type 2 diabetes (1). However, 55% to 70% of patients who initially achieve their glycemic targets with metformin therapy have a progressive deterioration of glucose control in 2 to 3 years (2). Sulfonylureas are a commonly used second medication (3) on the basis of efficacy (4), availability, and cost (5). However, adding a sulfonylurea to metformin therapy usually does not maintain long-term control, and deterioration develops in as early as 6 months (6). Options for third agents include insulin, α-glucosidase inhibitors (acarbose), thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 inhibitors (5, 7).

We report the findings of a meta-analysis to assess the comparative efficacy of these drug classes in the reduction of hemoglobin A_{1c} (HbA_{1c}) level, change in body weight, and the frequency of severe hypoglycemic events when added as a third agent to the treatment of patients with uncontrolled type 2 diabetes who are already receiving metformin and a sulfonylurea. We did a conventional meta-analysis, but because the number of randomized trials directly comparing antihyperglycemic agents is limited, we also used indirect comparisons and network meta-analysis.

See also:

Print
Editors' Notes 673

Web-Only
Appendixes
Appendix Table
Appendix Figures
CME quiz
Conversion of graphics into slides

METHODS

The review protocol was registered at the Conselho Nacional de Desenvolvimento Científico e Tecnológico Web site (www.cnpq.br).

Identification of Trials

We searched MEDLINE, EMBASE, Cochrane Library, LILACS, and ClinicalTrials.gov from 1950 to De-

cember 2010 by using the Medical Subject Heading terms *type 2 diabetes*, *noninsulin antihyperglycemic agents* and *insulins*, and by using a validated filter (8) to identify randomized, controlled trials reporting the effect on HbA_{1c} level of adding a third noninsulin antihyperglycemic agent or insulin to metformin and sulfonylurea in patients with type 2 diabetes. The MEDLINE search strategy is detailed in **Appendix 2** (available at www.annals.org). All potentially eligible trials were considered for review, regardless of the primary outcome or language. A manual search was also done by using references of key articles published in English. The data of 1 study identified in ClinicalTrials.gov (but not published) obtained directly from the authors.

Studies were considered eligible for inclusion if they were conducted in adults aged 18 years or older with type 2 diabetes and an HbA_{1c} level greater than 7.0% while receiving metformin (≥1000 mg/d or maximum tolerated dose) and a sulfonylurea (≥50% of the maximum labeled dose) for at least 3 months before the screening visit, compared the effects of adding a third noninsulin antihyperglycemic agent or insulin to another agent or placebo in patients who were already receiving metformin and a sulfonylurea, had at least 24 weeks of follow-up, and reported changes in HbA_{1c} level and weight and numbers of patients with severe hypoglycemic reactions as defined by the investigator or as reactions requiring third-party assistance or blood glucose levels of 1.9 mmol/L (35 mg/dL) or less. Insulins were considered as a class and included human as well as analogue insulins. Studies comparing 2 formulations of insulins as a third agent in both groups were excluded.

Study Selection, Data Extraction, and Quality Assessment

Two independent investigators reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text evaluation. Trials selected for detailed analysis and data extraction were analyzed by 2 investigators with an agreement value (κ) of 98%; disagreements were resolved by a third investigator.

We extracted data on the first author's name; year of trial publication; participant number, age, and sex; trial duration; drug class of the third antihyperglycemic agent added; change in HbA_{1c} level (mean [SD]); change in body weight; and number of severe hypoglycemic reactions. Two independent and blinded reviewers evaluated risk for bias according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations (9).

Data Synthesis and Analysis

Direct Meta-analysis

We analyzed HbA_{1c} level and weight as continuous variables and reported absolute differences between arithmetic means before and after interventions. We reported the absolute number of severe hypoglycemic episodes because the occurrence of 0 events in both groups of some studies precluded the calculation of an overall odds ratio (10).

We used the Cochran Q test to evaluate heterogeneity between studies and considered a threshold P value less than 0.1 as statistically significant. We also did I^2 testing to evaluate the magnitude of the heterogeneity between studies (11). We calculated pooled estimates of the mean differences in HbA_{1c} level and weight between intervention groups by using a random-effects model (DerSimonian–Laird method) to adequately account for the additional uncertainty associated with study–study variability in the effect of different agents. We used random-effects meta-regression analyses to assess whether diabetes duration, baseline HbA_{1c} level, baseline body mass index (BMI), and industry funding were potential sources of heterogeneity by using the restricted maximum likelihood estimator. We chose variables on the basis of previous data (12, 13) or biological relevance before the meta-analysis was undertaken. We assessed the possibility of publication bias by using a funnel plot of each trial's effect size against the SE. We evaluated funnel plot asymmetry by using Begg and Egger tests and defined significant publication bias as a P value less than 0.1 (14). The direct meta-analysis was done by using Stata statistical software, version 11.0 (StataCorp, College Station, Texas).

Network Meta-analysis

We also used network meta-analyses because no trials compared the effect of all antihyperglycemic agents used as a third drug with each other. This approach makes use of direct comparisons from existing trials comparing 2 treat-

Context

Metformin and sulfonylureas are inexpensive, first-line therapies for type 2 diabetes but are often insufficient to control blood glucose levels.

Contribution

This analysis of 18 trials found that all other available drugs decreased hemoglobin A_{1c} levels about equally when added to metformin and a sulfonylurea, without any clear between-drug differences. Insulin was associated with more weight gain and hypoglycemia.

Caution

Most trials were short, trial quality varied, and many comparisons of effect were indirect.

Implication

Available evidence suggests no clear differences in benefit between drugs when adding a third agent to metformin and a sulfonylurea. The choice should be based on patient preferences and characteristics.

—The Editors

ment strategies and indirect comparisons constructed from 2 trials that have at least 1 treatment in common (15). This statistical tool preserves the within-trial, randomized comparison of each study. Network analyses were conducted by using a Bayesian Markov-chain Monte Carlo method and fitted in the freely available Bayesian software WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom; www.mrc-bsu.cam.ac.uk/bugs). Results are expressed as mean differences with 95% credible intervals (CrIs) (the Bayesian equivalent of CIs). The estimated uncertainties in the ranking of treatments were calculated directly from the simulated posterior distribution generated by using the Markov-chain Monte Carlo analysis. The WinBUGS code is available from the authors on request.

Role of the Funding Source

The study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Projeto Nacional de Pós-Doutorado no País. The funding sources had no role in the study design, data collection, data analyses, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and was responsible for making the final decision to submit the manuscript for publication.

RESULTS

Literature Search Results and Study Characteristics

We identified 23 921 studies through electronic searches and 42 through manual searches (**Appendix Figure 1**, available at www.annals.org). Of these, 23 843 were excluded on the basis of the title and abstract, leaving 120 studies for further evaluation. Eighteen studies fulfilled our inclusion criteria, providing data on 4535 participants (16–32). We obtained data directly from the authors for 1 unpublished trial. Because another trial compared 2 classes of noninsulin antihyperglycemic agents with placebo, 19 sets of comparisons were available for analyses.

Table 1 summarizes the randomized, controlled trials. The trials were published from 1998 to 2009 and varied in sample size. Trial duration ranged from 24 to 52 weeks (mean, 31.3 weeks). The 4535 patients had a mean baseline HbA_{1c} level of 8.8% (7.5% to 10.6%), a mean baseline BMI of 28.8 kg/m^2 (24.0 kg/m^2 to 34.2 kg/m^2), and diabetes duration of 8.9 years (8.1 to 13.6 years). Nine reports compared active drugs (noninsulin antihyperglycemic agents or insulins) with placebo, and 10 trials compared noninsulin antihyperglycemic agents with insulins.

The **Appendix Table** (available at www.annals.org) shows the risk for bias in the trials. Nine studies reported adequate randomization, 0 were stopped early, and 15 did not specify whether data collectors and outcome assessors were blinded to study data. There was no evidence of publication bias when HbA_{1c} level was used as an outcome (**Appendix Figure 2**, available at www.annals.org).

Direct Meta-analysis

All classes of antihyperglycemic agents were associated with statistically significant reductions in HbA_{1c} level compared with placebo. In a pooled analysis (9 trials), the addition of a third agent led to a mean reduction of −0.96% (95% CI, −1.11% to −0.81%) in HbA_{1c} level (**Table 2**), with statistically significant between-study heterogeneity ($I^2 = 63.7\%$; $P = 0.005$). Change in HbA_{1c} level was seen with each antihyperglycemic class, varying from −0.60% (CI, −1.16% to −0.04%) for acarbose to −1.15% (CI, −1.35% to −0.95%) for thiazolidinediones. In meta-regression analysis, baseline HbA_{1c} level, diabetes duration, and baseline BMI were not associated with a change in HbA_{1c} level ($P = 0.19$).

In a pooled analysis of trials comparing noninsulin antihyperglycemic agents with insulin (10 trials), treatment with noninsulin antihyperglycemic agents led to a mean 0.29% increase in HbA_{1c} level (CI, 0.06% to 0.51%) compared with insulins, with statistically significant between-study heterogeneity ($I^2 = 73.4\%$; $P < 0.001$). In meta-regression analysis, baseline HbA_{1c} level, diabetes duration, baseline BMI, and industry funding were not associated with a change in HbA_{1c} level ($P = 0.08$).

Weight change varied by drug class. Compared with placebo, insulin led to a statistically significant increase in weight (2.31 kg [CI, 0.13 to 4.48 kg]), whereas acarbose led to a statistically significant decrease in weight (−0.96 kg [CI, −1.80 to −0.12 kg]) (**Table 2**). Compared with insulins, thiazolidinediones were associated with weight increase (1.67 kg [CI, 0.98 to 2.36 kg]), and GLP-1 agonists led to a weight decrease (−4.99 kg [CI, −5.80 to −4.18 kg]).

We could not meta-analyze the frequency of hypoglycemic episodes because severe hypoglycemia was not reported in either study group in several trials. As expected, insulins doubled the risk for severe hypoglycemic episodes when compared with noninsulin antihyperglycemic agents (**Table 2**).

Network Meta-analysis

Figure 1 shows the network of comparisons, and **Table 3** estimates HbA_{1c} level and weight change for each comparison. The change in HbA_{1c} level ranged from −0.7% (95% CrI, −1.33% to −0.08%) for acarbose to −1.08% (CrI, −1.41% to −0.77%) for insulin compared with placebo. There were no statistically significant differences between agents in pairwise comparisons. Weight loss was statistically significant for GLP-1 agonists compared with placebo (−1.63 kg [CrI, −2.71 to −0.06 kg]) and for acarbose compared with insulin (−3.79 kg [CrI, −5.91 to −1.88 kg]) and thiazolidinediones (−5.21 kg [CrI, −7.53 to −2.98 kg]). Weight gain was statistically significant for insulin compared with placebo and GLP-1 agonists and for thiazolidinediones compared with placebo, GLP-1 agonists, and insulin.

Table 1. **Summary of Randomized, Controlled Trials of Antihyperglycemic Drugs Added as a Third Agent in the Treatment of Patients With Type 2 Diabetes Who Are Receiving Metformin and a Sulfonylurea**

Study, Year (Reference), by Drug Type	Follow-up, *wk*	Group	Patients, *n*	Mean Age (SD), *y*	Men, %	Mean Diabetes Duration (SD), *y*	Mean Baseline HbA_{1c} Level (SD), %	Mean Baseline BMI (SD), *kg/m²*	Mean Change in HbA_{1c} Level (SD), %	Mean Change in Weight (SD), *kg*	Severe Hypoglycemia, *n*
Acarbose											
Lam et al, 1998 (16)	24	Placebo	40	56.9 (1.3)	56.8	10.1 (0.8)	9.4 (0.1)	24.1 (0.4)	0.1 (1.3)	0.4 (1.8)	0
		Acarbose	41	57.8 (1.3)	55.5	10.1 (0.7)	9.5 (0.1)	24.8 (0.5)	−0.5 (1.3)	−0.5 (2.0)	1
Ko et al, 2001 (17)	52	NPH insulin	30	59.1 (12.5)	30.0	13.3 (6.1)	10.0 (0.8)	24.9 (3.4)	−1.7 (1.3)	NA	NA
		Acarbose	27	58.5 (9.9)	37.0	9.7 (6.2)	10.6 (1.7)	24.3 (3.8)	−1.5 (1.8)	NA	NA
Thiazolidinediones											
Yale et al, 2001 (18)	24	Placebo	99	60 (0.9)	58.0	10.8 (0.6)	9.7 (0.1)	30.0 (0.4)	0 (1.0)	−0.1 (15.2)	0
		Troglitazone	101	58 (0.9)	55.0	11.9 (0.8)	9.6 (0.1)	30.1 (0.5)	−1.4 (2.0)	2.3 (14.0)	0
Dailey et al, 2004 (19)	24	Placebo	184	57 (10)	61.0	9.0 (6.0)	8.1 (0.8)	32.0 (5.0)	0.1 (1.0)	0.1	0
		Rosiglitazone	181	57 (9)	58.0	9.0 (7.0)	8.1 (0.9)	32.0 (5.0)	−0.9 (1.2)	3.0	0
Kadoglou et al, 2008 (28)	26	Placebo	35	66.7 (9.6)	45.7	7.5 (5.9)	8.0 (0.8)	29.9 (4.3)	0.3 (0.6)	NA	NA
		Rosiglitazone	35	63.8 (7.3)	40.0	8.5 (4.6)	8.2 (1.2)	29.5 (3.8)	−0.9 (0.4)	NA	NA
Ko et al, 2006 (22)	48	NPH insulin	56	59.8 (11.2)	42.9	13.6 (7.5)	9.6 (0.9)	24.0 (2.7)	−1.3 (1.7)	NA	0
		Rosiglitazone	56	56.6 (10.7)	57.1	11.8 (7.7)	10.1 (1.0)	25.3 (3.8)	−1.1 (1.6)	NA	0
Rosenstock et al, 2006 (23)	24	Glargine insulin	104	55.9 (10.5)	45.0	8.5 (5.8)	8.8 (1.0)	34.6 (7.0)	−1.7 (0.9)	1.7 (4.0)	3
		Rosiglitazone	112	55.3 (11.4)	58.0	8.1 (5.1)	8.7 (1.0)	33.6 (6.3)	−1.5 (0.9)	3.0 (4.2)	6
Reynolds et al, 2007 (26)	24	Glargine insulin	20	NA	NA	NA	8.9 (0.9)	32.4 (5.3)	−1.4 (1.3)	0.9 (1.0)	0
		Rosiglitazone	20	NA	NA	NA	9.1 (0.9)	30.7 (5.1)	−1.5 (1.4)	3.2 (2.2)	0
Dorkhan et al, 2008 (27)	26	Glargine insulin	19	61.9 (7.7)	68.4	9.5 (6.8)	8.2 (1.3)	31.4 (5.7)	−2.2 (1.5)	2.4 (20.0)	0
		Pioglitazone	17	60.8 (7.1)	76.4	11.5 (6.1)	8.1 (1.4)	30.6 (5.3)	−1.3 (1.4)	3.3 (11.9)	0
Hartemann-Heurtier et al, 2009 (31)	24	NPH insulin	13	58 (10)	64.2	12.0 (6.0)	8.6 (0.5)	32.0 (4.0)	−1.6 (0.5)	2.4 (1.7)	0
		Pioglitazone	14	62 (10)	53.8	12.0 (4.5)	8.3 (0.5)	30.0 (5.0)	−1.2 (0.7)	3.7 (3.5)	0
Rosenstock et al*	48	Exubera†	203	54.2 (9.5)	57.6	10.2	9.2 (1.0)	31.3 (4.7)	−1.7 (1.3)	5.0 (18.0)	3
		Rosiglitazone	202	55.0 (9.4)	55.0	10.0	9.0 (1.1)	31.3 (4.5)	−1.5 (1.2)	5.2 (19.0)	0
GLP-1 agonists											
Kendall et al, 2005 (21)	30	Placebo	247	56 (10)	55.9	9.4 (6.2)	8.5 (1.0)	34.0 (5.0)	0.2 (1.6)	−0.9 (3.1)	0
		Exenatide	241	55 (10)	59.3	8.7 (6.4)	8.5 (1.1)	34.0 (6.0)	−0.8 (1.5)	−1.6 (3.1)	0
Heine et al, 2005 (20)	26	Glargine insulin	267	58 (9.5)	56.6	9.2 (5.7)	8.3 (1.0)	31.3 (4.6)	−1.1 (1.6)	1.8 (3.2)	4
		Exenatide	282	59.8 (8.8)	55.0	9.9 (6.0)	8.2 (1.0)	31.4 (4.4)	−1.1 (1.6)	−2.3 (3.3)	4
Nauck et al, 2007 (25)	52	Premixed aspart (30%)	248	58 (9)	51.0	10 (6.2)	8.6 (1.1)	30.2 (4.2)	−0.9 (0.9)	2.9 (3.1)	0
		Exenatide	253	59 (9)	47.0	9.8 (6.3)	8.6 (1.0)	30.6 (4.0)	−1.0 (1.1)	−2.5 (3.2)	0
Bergenstal et al, 2009 (29)	24	Premixed aspart (30%) once daily	124	51.8 (10.9)	48.4	8.4 (6.3)	10.1 (1.8)	33.7 (7.1)	−2.3 (1.5)	2.8 (3.6)	4
		Premixed aspart (30%) twice daily	124	53.4 (9.96)	47.6	9.9 (5.6)	10.3 (1.9)	33.5 (7.4)	−2.8 (1.8)	4.1 (5.4)	6
		Exenatide	124	52.5 (10.62)	48.4	8.6 (5.9)	10.2 (1.5)	34.2 (7.1)	−1.7 (1.6)	−1.9 (3.8)	0
Russell-Jones et al, 2009 (32)	26	Placebo	114	57.5 (9.6)	49.0	9.4 (6.2)	8.3 (0.9)	31.3 (5.0)	−0.2 (1.2)	0.4 (4.2)	0
		Glargine insulin	232	57.5 (10.5)	60.0	9.7 (6.4)	8.2 (0.9)	30.3 (5.3)	−1.1 (1.4)	1.6 (5.0)	0
		Liraglutide	230	57.6 (9.5)	57.0	9.2 (5.8)	8.3 (0.9)	30.4 (5.3)	−1.3 (1.4)	−1.8 (5.0)	5
DPP-4 inhibitors											
Hermansen et al, 2007 (24)	24	Placebo	116	57.7 (8.9)	52.2	10.6 (6.8)	8.3 (0.7)	30.7 (6.2)	0.3 (0.9)	NA	0
		Sitagliptin	113	56.6 (8.8)	52.6	9.3 (5.7)	8.3 (0.7)	31.3 (5.9)	−0.6 (0.8)	NA	0
Insulins											
Blicklé et al, 2009 (30)	36	Lifestyle changes	108	60.7 (8.1)	50.0	10.1 (6.9)	7.5 (0.4)	29.9 (3.4)	−0.2 (0.9)	−2.5 (3.2)	0
		Glargine insulin	103	60.6 (7.7)	55.0	10.0 (6.2)	7.6 (0.7)	30.1 (3.5)	−0.8 (0.7)	0.9 (2.9)	2

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available; NPH = neutral protamine Hagedorn.
* Unpublished report (in preparation).
† Pfizer (New York, New York); no longer on the market.

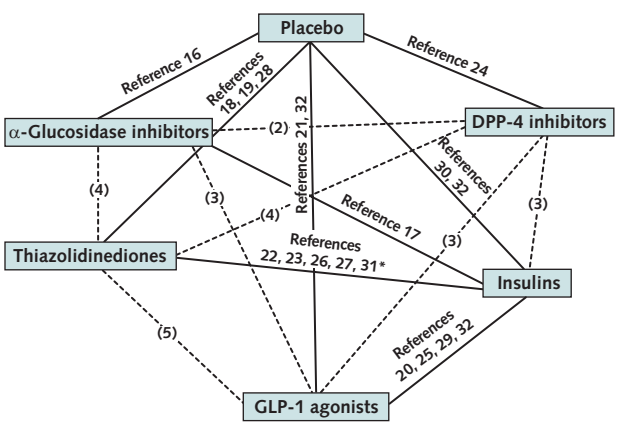
Table 2. **Direct Meta-analysis Comparing Noninsulin Antihyperglycemic Agents or Insulins With Placebo and Noninsulin Antihyperglycemic Agents With Insulins: Effects on Change in HbA_{1c} Level and Weight and Severe Hypoglycemic Episodes**

Reports, *n*	Intervention	Weighted Mean Difference (95% CI) in HbA_{1c} Level, %	Weighted Mean Difference (95% CI) in Weight, *kg*	Severe Hypoglycemic Episodes (Events/Total), *n/n*	
				Intervention	Placebo or Insulin
Noninsulin antihyperglycemic agents or insulins vs. placebo					
9*	All agents	−0.96 (−1.11 to −0.81)	0.37 (−1.46 to 2.20)	8/1233	0/1016
2	Insulin	−0.71 (−0.95 to −0.47)	2.31 (0.13 to 4.48)	2/335	0/222
3†	Thiazolidinediones	−1.15 (−1.35 to −0.95)	2.40 (−1.65 to 6.45)	0/278	0/277
1	Acarbose	−0.60 (−1.16 to −0.04)	−0.96 (−1.80 to −0.12)	1/41	0/40
2	GLP-1 agonists	−1.04 (−1.24 to −0.85)	−1.40 (−2.90 to 0.08)	5/466	0/361
1	DPP-4 inhibitors	−0.89 (−1.11 to −0.67)	NA	0/113	0/116
Noninsulin antihyperglycemic agents vs. insulins					
10‡	All agents	0.29 (0.06 to 0.51)	−1.90 (−3.73 to −0.06)	6/553	15/566
6§	Thiazolidinediones	0.22 (0.07 to 0.37)	1.67 (0.98 to 2.36)	3/415	9/421
1	Acarbose	0.20 (−0.60 to 1.00)	NA	NA	NA
3	GLP-1 agonists	0.10 (−0.28 to 0.42)	−4.99 (−5.80 to −4.18)	3/138	6/145

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.
* Six studies reported a change in body weight.
† One study reported a change in body weight, and 2 studies reported hypoglycemic episodes.
‡ Nine studies reported a change in body weight.
§ Five studies reported a change in body weight.

Figure 2 summarizes the estimated probability that a given drug class is the next best one to reduce levels of HbA_{1c} (*left*) or to avoid weight gain (*right*), given available trial data.

Figure 1. **Network of clinical trials of antihyperglycemic agents in addition to metformin and a sulfonylurea in patients with type 2 diabetes.**



Solid lines represent direct comparison trials, and dashed lines represent indirect comparisons having placebo as the reference agent. Reference numbers indicate the trials contributing to direct comparisons. The number of studies that contribute for the indirect effect estimates are shown in parentheses. DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.
* These references also include an unpublished report by Rosenstock and colleagues (in preparation).

DISCUSSION

In this meta-analysis of trials evaluating the effects of adding a third antihyperglycemic agent to metformin and sulfonylurea therapy for patients with type 2 diabetes, we report an overall reduction of HbA_{1c} level of −0.96%, a finding similar to that of a recent network meta-analysis (7) that reported an overall reduction of HbA_{1c} level of −0.62% to −1.00% when a second drug was added to metformin therapy. We found no clear statistically significant differences in the degree of reduction of HbA_{1c} level by drug class in direct and indirect comparisons, also confirming findings from the previous analysis, although it did not evaluate insulin efficacy (7). A similar decrease (−0.5% to −1.25%) was seen in a meta-analysis comparing the effect of adding a single oral antidiabetic agent (GLP-1 agonists and insulins were not evaluated) versus placebo in participants who either were drug-naive or were receiving background therapy with an oral antidiabetic agent with or without insulin (13). Taken together, these findings suggest that addition of a third antihyperglycemic agent provides useful additional glycemic control for patients who are already receiving metformin and a sulfonylurea. The available limited evidence does not clearly identify a preferred antihyperglycemic drug class among drugs represented in clinical trials (thiazolidinediones, GLP-1 agonists, dipeptidyl peptidase-4 inhibitors, insulins, and acarbose). Glucagon-like peptide-1 agonists led to more weight loss than other agents and might be chosen as a third agent on that basis, but they also were associated

Table 3. **Network Meta-analysis Comparing All Noninsulin Antihyperglycemic Agents and Insulins: Mean Changes in HbA_{1c} Level and Weight**

Treatment	Change in HbA_{1c} Level (95% CrI), %					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.01 (−1.38 to −0.66)	–	–	–	–	–
Insulin	−1.08 (−1.41 to −0.77)	−0.07 (−0.41 to 0.25)	–	–	–	–
Thiazolidinediones	−0.95 (−1.27 to −0.65)	0.05 (−0.35 to 0.5)	0.12 (−0.16 to 0.41)	–	–	–
DPP-4 inhibitors	−0.94 (−1.58 to −0.36)	0.07 (−0.6 to 0.67)	0.14 (−0.51 to 0.77)	0.01 (−0.67 to 0.69)	–	–
Acarbose	−0.70 (−1.33 to −0.08)	0.31 (−0.4 to 1.03)	0.38 (−0.28 to 1.06)	0.25 (−0.39 to 0.93)	0.24 (−0.56 to 1.13)	–
	Change in Weight (95% CrI), *kg*					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.63 (−2.71 to −0.60)	–	–	–	–	–
Insulin	2.84 (1.76 to 3.90)	4.47 (3.71 to 5.26)	–	–	–	–
Thiazolidinediones	4.25 (2.76 to 5.66)	5.89 (4.54 to 7.2)	1.42 (0.29 to 2.55)	–	–	–
DPP-4 inhibitors	NA	NA	NA	NA	–	–
Acarbose	−0.96 (−2.77 to 0.73)	0.67 (−1.37 to 2.63)	−3.79 (−5.91 to −1.88)	−5.21 (−7.53 to −2.98)	NA	–

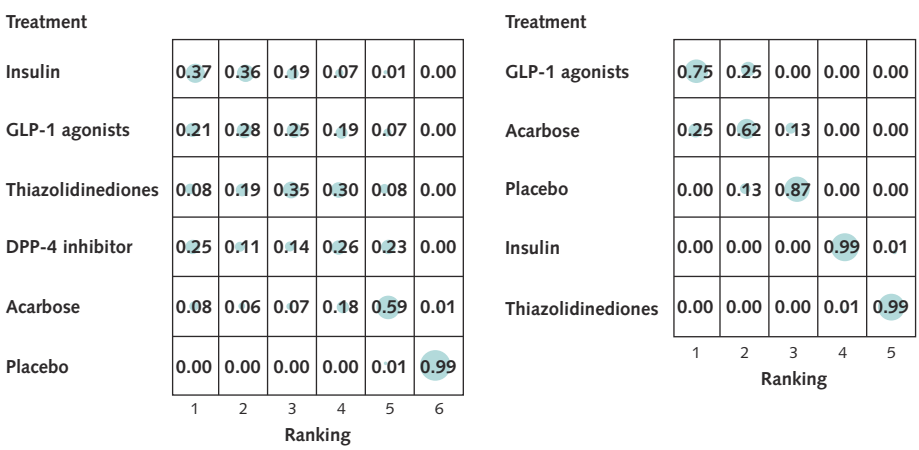
CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.

with more severe hypoglycemic reactions than any other drug class except insulin.

It is common in clinical practice to initiate insulin therapy after failure of therapies of 2 oral antihyperglycemic agents. In direct and network comparisons, insulins did not differ from other drug classes in their ability to decrease HbA_{1c} levels, although the point estimate of effect was slightly greater for insulins in our analysis of trials directly comparing insulins with other drug classes (difference in HbA_{1c}, 0.29% [CI, 0.06% to 0.51%]) (**Table 2**). In network meta-analysis, insulin ranked first in the probability of being the most effective. This apparent lack of superiority of insulin over other agents could be explained by the few trials comparing insulin with other agents (limited statistical power) and by the use of lower doses of insulin (about 20 IU/d) in trials comparing insulin with placebo, which may have contributed to an overall underestimation of the effect of insulin on HbA_{1c} level. Also, insulin-induced weight gain in these trials could have blunted the apparent benefits of the drugs.

There were statistically and clinically significant differences between drug classes in weight changes and incidence of severe hypoglycemia. Patients receiving GLP-1 agonists had the greatest weight reduction, a finding noted in a previous meta-analysis (7). Thiazolidinediones seemed to cause more weight gain (4.25 kg [CrI, 2.76 to 5.66 kg])

Figure 2. **Network meta-analysis of antihyperglycemic agents.**



Green dots account for the estimated probability (the higher the probability, the larger the dot). DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1. **Left.** The estimated probability that each treatment is ranked first, second, or third as the most effective for changing hemoglobin A_{1c} levels. **Right.** The estimated probability that each treatment is ranked first, second, or third as the most effective for avoiding an increase in weight.

than insulins (2.84 kg [CrI, 1.76 to 3.90 kg]), although the findings were not significantly different. Insulin doubled the frequency of severe hypoglycemic episodes. Other adverse events potentially related to the antihyperglycemic agents in this review (bone fracture; pancreatitis; and cardiovascular, gastrointestinal, and renal dysfunction) were not evaluated because of the lack of reporting data in most of the trials included in our meta-analysis.

Our analysis has many limitations. Most of the trials were short term, generally lasting less than 1 year, and none evaluated important clinical outcomes, such as cardiovascular events and death. The quality of trial conduct and reporting varied; only 5 of 18 studies included in the analyses were double-blind, and details of allocation were noted in only 9 of 18 studies, suggesting that other potential biases may have been introduced. Treatment regimens and patient populations varied, and we documented statistical heterogeneity that is unexplained by our meta-regression model, a reflection of unmeasured factors influencing the findings and the many different agents and classes of agents included in the trials.

Perhaps most important, the need to rely on indirect comparisons for most antihyperglycemic agents makes our conclusions tentative, and the fact that so few studies contributed evidence for so many of the indirect comparisons adds uncertainty about the relative effectiveness of these agents. For example, the evidence for the indirect comparison between α-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors comes from pairing only 2 studies that each used a placebo control as a comparator, whereas the indirect comparison of α-glucosidase inhibitors with thiazolidinediones used data from 1 study comparing α-glucosidase inhibitors with placebo and 3 studies that compare thiazolidinediones with placebo for this estimate. More trials would therefore be required before the indirect evidence about many of the comparisons could be considered robust.

Notwithstanding these important limitations, it is unlikely that the head-to-head trials necessary to address this clinical question will be conducted. There would need to be at least 13 trials to compare all classes of antihyperglycemic agents, and in their absence, our network meta-analysis seems a reasonable tool to ask and attempt to answer the question.

In summary, we conclude that there is no apparent difference in benefit between drug classes in patients with type 2 diabetes who are receiving metformin and a sulfonylurea and require a third antihyperglycemic agent. When choosing a third drug to be added to metformin and sulfonylurea therapy in patients requiring additional glycemic control, the patient's clinical features, such as importance of weight changes and incidence of hypoglycemia, should be taken into account. The most appropriate drug option should be individualized to each patient's clinical characteristics.

From Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Acknowledgment: The authors thank Solomon Klioze and Neville Jackson from Pfizer for providing unpublished data, John Stewart and Maria Isabel Vergani from Sanofi-Aventis for making supplemental data available, and Edison Gonçalves for his technical revision and useful suggestions.

Grant Support: From Conselho Nacional de Desenvolvimento Científico e Tecnológico grant A576627/2008-9 and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Programa Nacional de Pós-Doutorado no País 03021/09-2.

Potential Conflicts of Interest: Dr. Gross: *Board membership:* Bristol-Myers Squibb, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis, Eli Lilly; *Payment for development of educational presentations:* Bristol-Myers Squibb, Novo Nordisk, Eli Lilly. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-2318.

Requests for Single Reprints: Jorge L. Gross, MD, PhD, Division of Endocrinology of Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Prédio 12, 4th Floor, 90035-003, Porto Alegre-RS, Brazil; e-mail, jorgeluizgross@gmail.com.

Current author addresses and author contributions are available at www.annals.org.

References

1. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-65. [PMID: 9742977]

2. **Cook MN, Girman CJ, Stein PP, Alexander CM.** Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. Diabet Med. 2007;24:350-8. [PMID: 17335466]

3. **Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al; American Diabetes Association.** Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193-203. [PMID: 18945920]

4. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53. [PMID: 9742976]

5. **International Diabetes Federation.** Global Guideline for Type 2 Diabetes. Accessed at www.idf.org/node/1285?unode=B7462CCB-3A4C-472C-80E4-710074D74AD3 on 3 April 2011.

6. **Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR.** Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. Diabetes Care. 2005;28:995-1000. [PMID: 15855556]

7. **Phung OJ, Scholle JM, Talwar M, Coleman CI.** Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303:1410-8. [PMID: 20388897]

8. **Robinson KA, Dickersin K.** Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol. 2002;31:150-3. [PMID: 11914311]

9. **Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al.** The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65-94. [PMID: 19622512]

10. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med.

2004;23:1351-75. [PMID: 15116347]
11. **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58. [PMID: 12111919]
12. **Bekelman JE, Li Y, Gross CP.** Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289:454-65. [PMID: 12533125]
13. **Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC.** The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010;33:1859-64. [PMID: 20484130]
14. **Begg CB, Mazumdar M.** Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101. [PMID: 7786990]
15. **Lu G, Ades AE.** Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105-24.
16. **Lam KS, Tiu SC, Tsang MW, Ip TP, Tam SC.** Acarbose in NIDDM patients with poor control on conventional oral agents. A 24-week placebo-controlled study. Diabetes Care. 1998;21:1154-8. [PMID: 9653611]
17. **Ko GT, Tsang CC, Ng CW, Wai HP, Kan EC.** Use of acarbose or bedtime insulin after failure of treatment with conventional oral antidiabetics: a one-year randomised clinical trial. Clin Drug Investig. 2001;21:401-8.
18. **Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL.** The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134:737-45. [PMID: 11329231]
19. **Dailey GE 3rd, Noor MA, Park JS, Bruce S, Fiedorek FT.** Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004;116:223-9. [PMID: 14969649]
20. **Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group.** Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143:559-69. [PMID: 16230722]
21. **Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al.** Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28:1083-91. [PMID: 15855571]
22. **Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC.** Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. Adv Ther. 2006;23:799-808. [PMID: 17142216]
23. **Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G.** Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care. 2006;29:554-9. [PMID: 16505505]
24. **Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group.** Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007;9:733-45. [PMID: 17593236]
25. **Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al.** A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia. 2007;50:259-67. [PMID: 17160407]
26. **Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR.** Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract. 2007;77:180-7. [PMID: 17239474]
27. **Dorkhan M, Frid A, Groop L.** Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes: what to add—insulin glargine or pioglitazone? Diabetes Res Clin Pract. 2008;82:340-5. [PMID: 18926586]
28. **Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Liapis CD, Alevizos M.** Beneficial effects of rosiglitazone on novel cardiovascular risk factors in patients with type 2 diabetes mellitus. Diabet Med. 2008;25:333-40. [PMID: 18307460]
29. **Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V; NovoLog Mix-vs. Exenatide Study Group.** Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Curr Med Res Opin. 2009;25:65-75. [PMID: 19210140]
30. **Blicklé JF, Hancu N, Piletic M, Profozic V, Shestakova M, Dain MP, et al.** Insulin glargine provides greater improvements in glycaemic control vs. intensifying lifestyle management for people with type 2 diabetes treated with OADs and 7-8% A1c levels. The TULIP study. Diabetes Obes Metab. 2009;11:379-86. [PMID: 19087105]
31. **Hartemann-Heurtier A, Halbron M, Golmard JL, Jacqueminet S, Bastard JP, Rouault C, et al.** Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract. 2009;86:37-43. [PMID: 19683825]
32. **Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group.** Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52:2046-55. [PMID: 19688338]

Current Author Addresses: Drs. Gross, Kramer, Leitão, Viana, Schaan, Pinto, Rodrigues, and Azevedo and Mr. Hawkins: Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Prédio 12, 4th Floor, 90035-003, Porto Alegre-RS, Brazil.

Author Contributions: Conception and design: J.L. Gross, C.B. Leitão, M.J. Azevedo.
Analysis and interpretation of the data: J.L. Gross, C.K. Kramer, C.B. Leitão, N. Hawkins.
Drafting of the article: J.L. Gross, C.K. Kramer, C.B. Leitão, M.J. Azevedo.
Critical revision of the article for important intellectual content: J.L. Gross, C.K. Kramer, C.B. Leitão, M.J. Azevedo.
Final approval of the article: J.L. Gross, C.K. Kramer, C.B. Leitão, L.V. Viana, B.D. Schaan, T.C. Rodrigues, M.J. Azevedo.
Provision of study materials or patients: L.C. Pinto.
Statistical expertise: C.K. Kramer, N. Hawkins.
Obtaining of funding: M.J. Azevedo.
Collection and assembly of data: C.B. Leitão, T.C. Rodrigues, L.C. Pinto, L.V. Viana, C.K. Kramer.

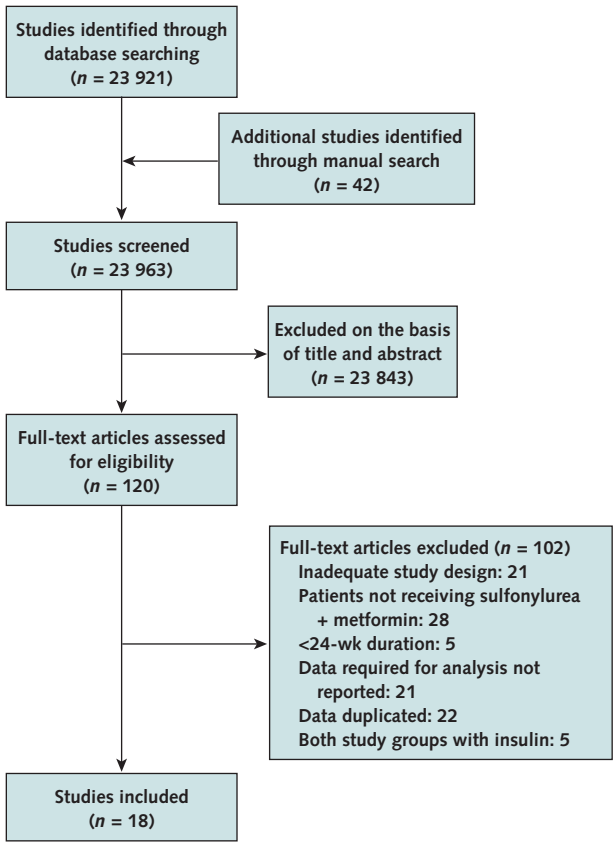
Appendix 1: Diabetes and Endocrinology Meta-analysis Group (DEMA)

Sandra P. Silveiro, MD, PhD; Rogério Friedman, MD, PhD; Luís H. Canani, MD, PhD; Themis Zelmanovitz, MD, PhD; Joíza L. Camargo, BC, PhD; Daisy C. Moreira, PhD; Fernando Gerchman, MD, PhD; Gabriele C. Ghisleni, PhD; Denise Sortica; Alessandra Zucatti; Thais Steemburgo, RD, PhD; João S. Felício, MD; Flávia Santos, MD; Ana R. Motta; Hermelinda C. Pedrosa, MD; Flaviene A. Prado, MD; Leonardo G. Miranda, MD; Monica T. Felix; Antonio R. Chacra, MD, PhD; Ana B. Valverde, MD; Marcelo A. Alvarenga, MD; William R. Komatsu, MD; Deborah L. Jezini, MD; Tatiane P. Oliveira, MD; Adriana C. Forti, MD; Ana L. Leitão Ramos, MD; Mirela C. Miranda; Marília B. Gomes, MD; Carisi A. Polanczyk, MD, PhD; Cristina Neumann, MD, PhD; and Otávio Berwanger, MD, PhD.

Appendix 2: MEDLINE Search Strategy

#1 "Diabetes Mellitus, Type 2"[Mesh] AND #2 ((((“Acarbose”[Mesh] OR “acarbose byproduct, component C” [Substance Name] OR “acarbose 7-phosphotransferase” [Substance Name] OR “acarbose 7-phosphate” [Substance Name])) OR “pramlintide” [Substance Name]) OR “3-hydroxyadamantylglycine-4,5-methanoprolinenitrile” [Substance Name]) OR “alogliptin” [Substance Name] OR ((((((((((((((((((“Metformin”[Mesh] OR “tetrachloro(metformin)platinum(IV)” [Substance Name])) OR “Sulfonylurea Compounds”[Mesh]) OR (“Glyburide”[Mesh] OR “4-transhydroxy glyburide” [Substance Name])) OR (“glimepiride” [Substance Name] OR “hydroxyglimepiride” [Substance Name])) OR (“Tolbutamide”[Mesh] OR “tolbutamide 4-hydroxylase” [Substance Name] OR “carboxytolbutamide” [Substance Name])) OR “Gliclazide”[Mesh]) OR “Chlorpropamide”[Mesh]) OR (“rosiglitazone” [Substance Name] OR “rosiglitazone-metformin combination” [Substance Name])) OR “pioglitazone” [Substance Name]) OR “Thiazolidinediones-”[Mesh]) OR (“troglitazone” [Substance Name] OR “5-(4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl)-2,4-dioxothiazollidine, troglitazone dihydrate” [Substance Name])) OR “exenatide” [Substance Name]) OR “liraglutide” [Substance Name]) OR “vildagliptin” [Substance Name]) OR “sitagliptin” [Substance Name]) OR (“repaglinide” [Substance Name] OR “2-methoxy-4-(3-methyl-1-(2-piperidin-1-ylphenyl)butylcarbamoyl) benzoic acid” [Substance Name])) OR “nateglinide” [Substance Name]) OR “meglitinide” [Substance Name]) OR “Insulin-”[Mesh] AND #3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])

Appendix Figure 1. **Summary of evidence search and selection.**

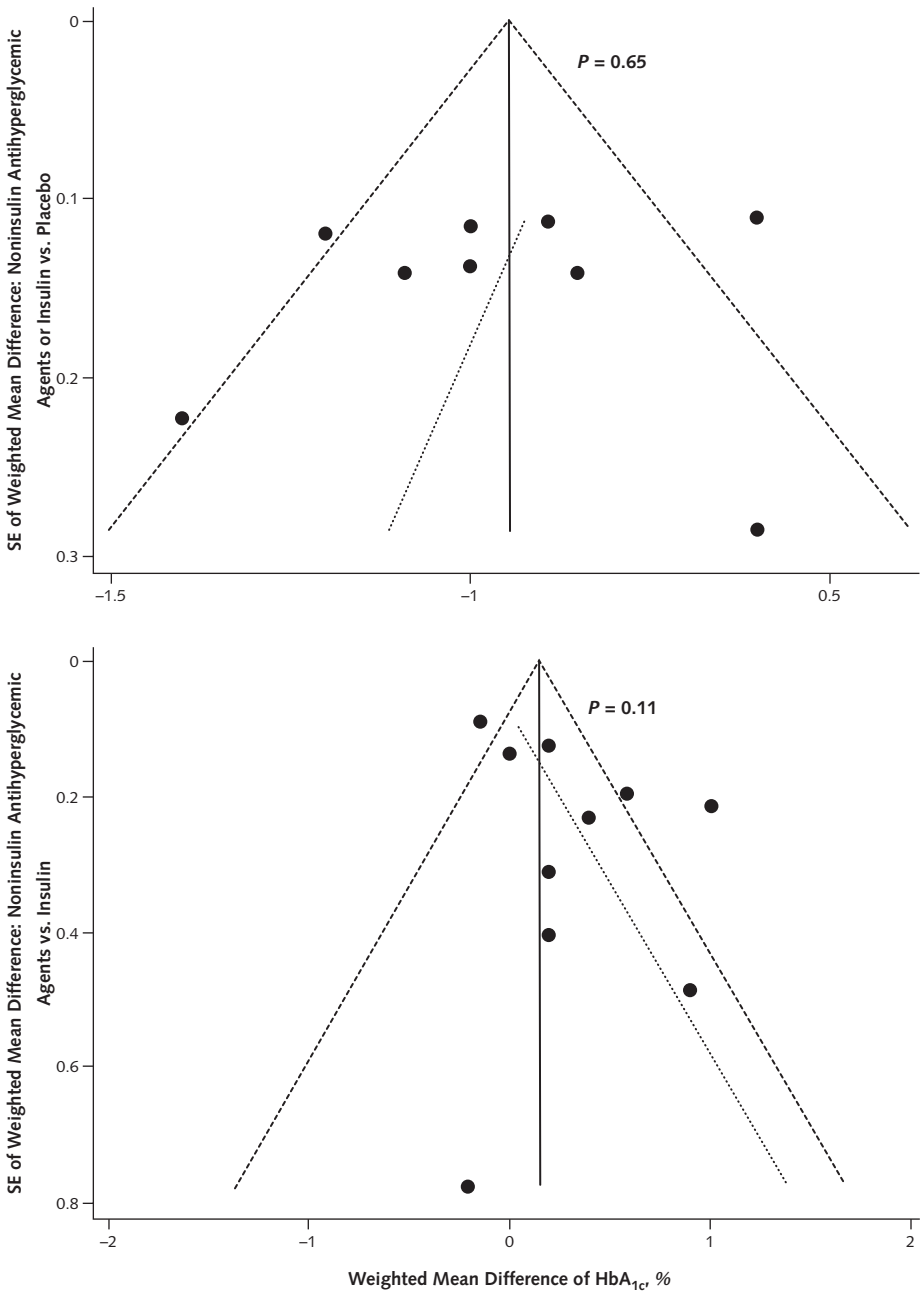


Appendix Table. **Risk for Bias Assessment in Randomized, Clinical Trials**

Study, Year (Reference)	Concealment of Randomization	Stopped Early	Patients Blinded	Health Care Providers Blinded	Data Collectors Blinded	Outcome Assessors Blinded
Lam et al, 1998 (16)	Not informed	No	Yes	Yes	Not informed	Not informed
Ko et al, 2001 (17)	Not informed	No	No	No	Not informed	Not informed
Yale et al, 2001 (18)	Yes	No	Yes	Yes	Yes	Yes
Dailey et al, 2004 (19)	Not informed	No	Yes	Yes	Not informed	Not informed
Heine et al, 2005 (20)	Yes	No	No	No	Not informed	Not informed
Kendall et al, 2005 (21)	Not informed	No	Yes	Yes	Not informed	Not informed
Ko et al, 2006 (22)	Not informed	No	No	No	Not informed	Not informed
Rosenstock et al, 2006 (23)	Not informed	No	No	No	Not informed	Not informed
Hermansen et al, 2007 (24)	Yes	No	Yes	Yes	Not informed	Not informed
Nauck et al, 2007 (25)	Yes	No	No	No	Not informed	Not informed
Reynolds et al, 2007 (26)	Not informed	No	No	No	Not informed	Not informed
Dorkhan et al, 2008 (27)	Not informed	No	No	No	Not informed	Not informed
Kadoglou et al, 2008 (28)	Not informed	No	No	No	Not informed	Not informed
Bergenstal et al, 2009 (29)	Yes	No	No	No	Not informed	Not informed
Blicklé et al, 2009 (30)	Yes	No	No	No	Not informed	Not informed
Hartemann-Heurtier et al, 2009 (31)	Yes	No	No	No	Not informed	Not informed
Russell-Jones et al, 2009 (32)	Yes	No	No	No	No	No
Rosenstock et al*	Yes	No	No	No	No	No

* Unpublished report (in preparation).

Appendix Figure 2. **Funnel plots of change in HbA_{1c} level with Egger regression line.**



HbA_{1c} = hemoglobin A_{1c}.