

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

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THE AMERICAN DIABETES ASSOCIATION (ADA) recommends metformin and lifestyle modifications for initial pharmacological therapy of type 2 diabetes mellitus (DM).¹ However, due to the progressive nature of the disease, most patients will require the use of combination pharmacological therapy to reach therapeutic goals. The ADA recommends adding a sulfonylurea or insulin when metformin monotherapy is insufficient to reach or maintain target goals.¹ The thiazolidinedione pioglitazone may be recommended when the risk of hypoglycemia is especially undesirable, and the glucagon-like peptide-1 (GLP-1) analog exenatide may be recommended if weight loss is a major goal of therapy.¹ Remaining drugs (glinides, α -glucosidase inhibitors [AGIs], and dipeptidyl peptidase-4 [DPP-4] inhibitors) get only cursory mention in the ADA guidelines due to limited data supporting their relative efficacy.¹

Much of the available literature in type 2 DM evaluates antidiabetic drugs as monotherapy or in combination with

Context Metformin is the recommended initial drug therapy for patients with type 2 diabetes mellitus (DM). However, the optimal second-line drug when metformin monotherapy fails is unclear.

Objective To determine the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsulin antidiabetic drugs in patients with type 2 DM not controlled by metformin alone.

Data Sources A literature search via MEDLINE (beginning in January 1950) and Cochrane CENTRAL through January 2010 and a manual search of references for additional relevant studies.

Study Selection Randomized controlled trials (RCTs) with at least 3 months' duration, evaluating noninsulin antidiabetic drugs added to metformin in patients experiencing an inadequate response to maximized and stable (≥ 4 weeks at ≥ 1500 mg or maximally tolerated dose) metformin therapy.

Data Extraction Inclusion/exclusion criteria; duration of patient follow-up; drug, dose, and schedule used; use of concurrent lifestyle modification; and baseline characteristics (age, sex, anthropometrics, glycated hemoglobin A_{1c} [HbA_{1c}], duration of DM, and metformin dose). End points collected included mean change in HbA_{1c}, proportion of patients achieving HbA_{1c} goal of less than 7%, change in weight, and incidence of hypoglycemia. Mixed-treatment comparison meta-analysis was used to calculate the weighted mean difference for changes from baseline in HbA_{1c} and body weight and relative risk (RR) of HbA_{1c} goal attainment and hypoglycemia, with associated 95% credible intervals.

Data Synthesis Overall, 27 RCTs (n = 11 198) were included. Mean (range) trial duration was 32 (12-52) weeks. The different classes of drugs were associated with similar HbA_{1c} reductions (range, 0.64%-0.97%) compared with placebo. Although use of thiazolidinediones, sulfonylureas, and glinides were associated with weight gain (range, 1.77-2.08 kg), glucagon-like peptide-1 analogs, α -glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors were associated with weight loss or no weight change. Sulfonylureas and glinides were associated with higher rates of hypoglycemia than with placebo (RR range, 4.57-7.50).

Conclusion When added to maximal metformin therapy, all noninsulin antidiabetic drugs were associated with similar HbA_{1c} reductions but differed in their associations with weight gain and risk of hypoglycemia.

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drugs other than metformin.^{2,3} However, the efficacy of an agent may be smaller when combined with another drug compared with the agent as monotherapy.² Furthermore, patients with uncontrolled disease while receiving metformin monotherapy may differ from those with uncontrolled DM while receiving other types of monotherapies either in individual patient characteristics or their disease progression, thereby affecting their response to different classes of drugs. Because the current recommendations from the ADA do not address these concerns, our goal was to evaluate the efficacy of antidiabetic drugs for second-line therapy in addition to stable doses of metformin in a mixed-treatment comparison meta-analysis. A mixed-treatment comparison method was selected specifically to allow the use of direct comparisons and the indirect estimates via a network of trials.

METHODS

Study Selection

A systematic literature search for all relevant articles through January 2010 was conducted in MEDLINE (beginning January 1950) and Cochrane CENTRAL. The search strategy combined the Medical Subject Headings and keywords *metformin* with terms for type 2 DM (*type 2 diabetes mellitus*, *T2DM*, *noninsulin dependent diabetes*, *NIDDM*) and for glycated hemoglobin A_{1c} (*glycosylated hemoglobin*, *hemoglobin A_{1c}*, *HbA_{1c}*, *A_{1c}*). No language restrictions were imposed. For our MEDLINE search, we used the Cochrane Collaboration's Highly Sensitive Search Strategy sensitivity maximizing version for randomized controlled trials (RCTs).⁴ A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies. When applicable, efforts were made to contact investigators for clarification or additional data. Two investigators (O.J.P. and C.I.C.) reviewed all potentially relevant articles independently.

Trials were included in the analysis if they (1) were parallel-design RCTs; (2) compared noninsulin antidiabetic

drugs with either placebo or another noninsulin antidiabetic drug in addition to metformin in all treatment groups; (3) treated patients for at least 12 weeks but no more than 52 weeks after randomization; (4) included only patients who showed inadequate response to stable metformin monotherapy at randomization; and (5) reported outcomes of glycated hemoglobin A_{1c} (HbA_{1c}).³ For the purposes of our meta-analysis, the criterion of stable metformin monotherapy was considered met if a study included patients who received a total metformin dose of at least 1500 mg/d maintained for at least the preceding 4 weeks before randomization or if the total dose was at least 1000 mg/d for at least the preceding 4 weeks before randomization (allowing a patient to have a lower dose only if specified as the maximally tolerated dose), as long as the mean metformin dose of enrolled patients was at least 1500 mg/d during the study.

Trials that included patients not previously taking metformin monotherapy (including those receiving sulfonylureas, thiazolidinediones, or other nonmetformin therapies) were eligible if they assigned patients to a metformin monotherapy titration and dose-stable period of at least 4 weeks before randomization. Trials were excluded if they evaluated the addition of more than 1 drug to metformin, participants were not considered to have inadequate response to a stable metformin monotherapy, participants were taking background therapies other than metformin, or they evaluated insulin. Although insulin is generally considered the most effective antidiabetic treatment in patients with type 2 DM, it was not evaluated in this mixed-treatment comparison because unlike other medications, it is conceivable that any degree of hyperglycemia can be corrected by insulin treatment, provided adequate doses are administered (because the therapeutic effect of insulin maintains a dose-response relationship in virtually any dose range).^{1,3}

Validity Assessment

Validity assessment was performed by using the Jadad scale.⁵ The Jadad scale assesses inherent controllers of bias by assessing randomization, double-blinding, and patient withdrawals. These individual components were assessed and an aggregate score was calculated for each included trial (0=weakest, 5=strongest). Trials scoring less than 3 were deemed to have lower methodological quality. All trials were reviewed and graded by 2 investigators (O.J.P. and J.M.S.) independently. Disagreement was resolved through discussion.

Data Abstraction

Two investigators (O.J.P. and J.M.S.), through use of a standardized tool, independently abstracted all data with disagreements resolved by discussion.⁴ The following information was sought from each trial (1) author identification; (2) year of publication; (3) study design and method quality; (4) sample size; (5) inclusion/exclusion criteria; (6) duration of follow-up; (7) drug, dose, and schedule used; (8) use of concurrent lifestyle modification (diet, exercise, or both); and (9) baseline characteristics (age, sex, anthropometrics, HbA_{1c}, duration of DM, and metformin dose). End points collected included mean change in HbA_{1c}, number of patients achieving HbA_{1c} goal of less than 7%, change in weight, and incidence of hypoglycemia.¹ In cases in which there was more than 1 published article on the same population, the longest duration of follow-up (between 12 and 52 weeks) was incorporated into the meta-analysis, although all records were maintained for determining study design characteristics.

Statistical Analysis

Traditional meta-analyses analyzing changes in HbA_{1c} and body weight as continuous variables were undertaken. Separate analyses were conducted for each class of oral antidiabetic drug. In all cases, weighted mean differences (WMDs) and associated 95% confidence intervals (CIs) were

calculated using a DerSimonian and Laird random-effects model.⁶ Net changes in each study variable were calculated as the difference between treatment groups in the changes (baseline – follow-up) in these mean values (also referred to as the change score). In instances where variances for net changes were not reported directly, they were calculated from CIs, *P* values, or individual variances. When the variance for paired differences was not reported, we calculated it from variances at baseline and at the end of follow-up.

As suggested by Follmann et al,⁷ we assumed a correlation coefficient of 0.5 between initial and final values. Achievement of HbA_{1c} goal of less than 7% and overall hypoglycemic events were meta-analyzed as dichotomous end points, with weighted averages reported as relative risks (RRs) and associated 95% CIs. Again, a DerSimonian and Laird random-effects model was used.⁶ The likelihood of statistical heterogeneity was assessed by using the *I*² statistic (*I*² > 50% was considered representative of important statistical heterogeneity). Traditional meta-analysis was performed by using StatsDirect statistical software version 2.4.6 (StatsDirect Ltd, Cheshire, England). *P* < .05 was considered statistically significant.

In addition to traditional meta-analysis, a mixed-treatment comparison meta-analysis was conducted to compare the different oral antidiabetic drug treatment classes (sulfonylureas, glinides, thiazolidinediones, AGIs, DPP-4 inhibitors, and GLP-1 analogs). Along with analyzing the direct within-trial comparisons between 2 treatments (such as thiazolidinediones vs placebo), the mixed-treatment comparison framework enables incorporation of indirect comparisons constructed from 2 trials that have 1 treatment in common, such as thiazolidinediones vs placebo and placebo vs sulfonylureas, allowing the indirect comparison of thiazolidinediones with sulfonylureas. This type of analysis safeguards the within-trial randomized treatment comparison of each

trial while combining all available comparisons between treatments. Mixed-treatment comparison analyses were conducted by using a Bayesian Markov chain Monte Carlo method and fitted in the freely available Bayesian software, WinBUGS (available at <http://www.mrc-bsu.cam.ac.uk/bugs>).^{8,9}

Mixed-treatment comparison methods were used to calculate the WMDs of HbA_{1c} and body weight, and RRs for achievement of HbA_{1c} goal of less than 7% and occurrence of hypoglycemia for all treatments relative to placebo (referent), with accompanying 95% credible intervals (CrIs). In all cases, a random-effects model was fitted. Residual deviance was calculated for each outcome. Within a Bayesian framework, a residual deviance that approximates the number of unconstrained data points within the model suggests a good fit.⁸

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

To assess the potential confounding effect of heterogeneity on our results, subgroup and sensitivity analyses were performed on the change in HbA_{1c} end point, by which trials were stratified by patient or trial characteristics and data from specific trials reanalyzed. Baseline disease severity was considered by performing subgroup analysis according to baseline HbA_{1c}, evaluating trials with baseline HbA_{1c} of less than 8% and those with baseline HbA_{1c} of 8% or more. Trials of shorter duration (12-24 weeks inclusive) and those of longer duration (>24 weeks) were analyzed separately in subgroup analyses. In addition, a sensitivity analysis was performed whereby the meta-analysis was reanalyzed, excluding studies with a Jadad score of less than 3.

RESULTS

Study Characteristics

Of the 410 nonduplicate citations identified from the literature search, 45 full-text articles were screened for eligibility (FIGURE). Assessment of the full-text articles revealed that 2 were not parallel-design RCTs and 12 did not evaluate patients receiving a stable dose of metformin. Thirty-one articles were eligible for inclusion, representing 27 unique RCTs.¹⁰⁻⁴⁰ Twenty-six articles reported a change in HbA_{1c}, 13 reported HbA_{1c} goal achieved, 15 reported a change in body weight, and 24 reported hypoglycemia. Nine studies were not included in the body weight analysis because measures of variance (SD, SE, or 95% CI) for changes in body weight were not reported in these studies.* Attempts to obtain this information from authors were unsuccessful.

A total of 27 RCTs (n = 11 198 participants; age range, 53-62 years; 23%-75% were men; mean [range] trial duration, 32 [12-52] weeks; and baseline HbA_{1c} range, 6.4%-9.3%) met all of the inclusion criteria (eTable; available at <http://www.jama.com>) and reported outcomes (TABLE 1). eFigure 1, eFigure 2, eFigure 3, eFigure 4, and eFigure 5 illustrate the network of clinical trials according to the comparison of specific classes of noninsulin antidiabetic drugs for the overall body of literature and for each outcome evaluated.

Change in HbA_{1c} and HbA_{1c} Goal

All classes of antidiabetic drugs were associated with statistically significant reductions in HbA_{1c} compared with placebo in both traditional and mixed-treatment comparison meta-analyses (TABLE 2, eFigure 2, and eFigure 6). In the mixed-treatment comparison meta-analysis, sulfonylureas (0.79% reduction; 95% CrI, 0.62%-0.97%), glinides (0.65% reduction; 95% CrI, 0.36%-0.97%), thiazolidinediones (0.85% reduction; 95% CrI, 0.66%-1.08%), AGIs (0.64% reduction; 95% CrI, 0.26%-1.03%),

*References 10, 12, 19, 25, 27, 28, 30, 31, 36, 40.

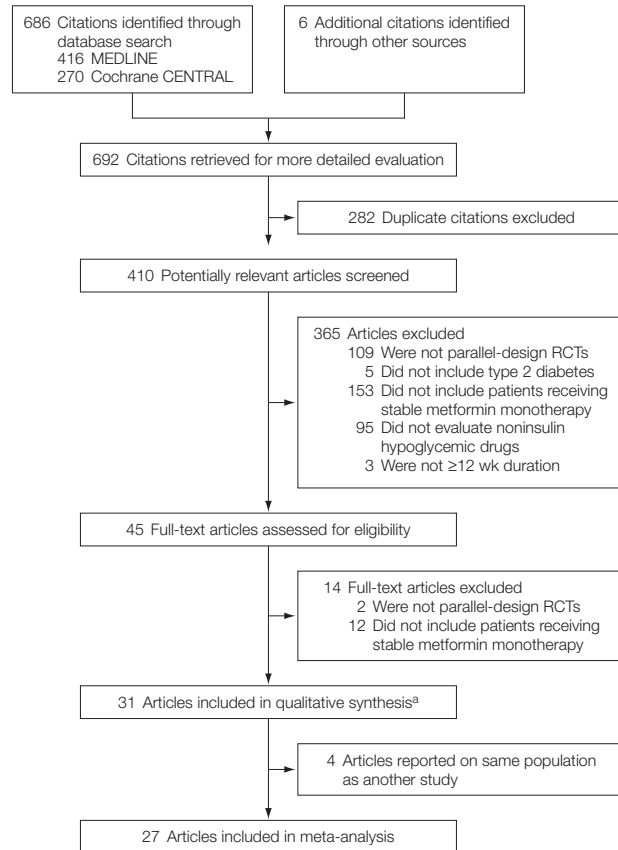
DPP-4 inhibitors (0.78% reduction; 95% CrI, 0.64%-0.93%), and GLP-1 analogs (0.97% reduction; 95% CrI, 0.65%-1.30%) were associated with significant reductions in HbA_{1c} compared with placebo. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (45 and 48, respectively). Review of funnel plots and Egger weighted regression statistic *P* values suggested a low likelihood of publication bias in all traditional analyses (all *P* > .25). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 2).

All classes of antidiabetic drugs were significantly more likely to achieve the HbA_{1c} goal compared with placebo in both traditional and mixed-treatment comparison meta-analyses (Table 2, eFigure 3, and eFigure 6). In mixed-treatment comparison meta-analysis, sulfonylureas (RR, 2.49; 95% CrI, 1.95-3.32), glinides (RR, 2.25; 95% CrI, 1.48-3.90), thiazolidinediones (RR, 2.71; 95% CrI, 1.74-3.80), DPP-4 inhibitors (RR, 2.51; 95% CrI, 2.04-3.22), and GLP-1 analogs (RR, 3.20; 95% CrI, 2.01-6.24) were associated with increased rates of achieving the HbA_{1c} goal. However, there were insufficient data to evaluate AGIs for this outcome. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (33 and 28, respectively). Re-

sults of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 3).

When evaluating the subgroup of studies in mixed-treatment comparison with baseline HbA_{1c} of less than 8%, we found an association with greater

Figure. Flow Diagram of RCTs Evaluating the Use of Noninsulin Antidiabetic Drugs Added to Metformin in Patients With Type 2 Diabetes



RCTs indicate randomized controlled trials.
^a Provided information about study design or patient demographics.

Table 1. Outcomes Reported by RCTs Evaluating Noninsulin Antidiabetic Drugs Added to Metformin in Patients With Type 2 Diabetes

Source	Follow-up, wk	Group	Change in HbA _{1c}		Achieved HbA _{1c} Goal <7% ^b	Change in Weight		Overall Hypoglycemia ^b
			No. ^a	Mean (SD), %		No. ^a	Mean (SD), kg	
DeFronzo, ¹⁰ 2009	24	DPP-4 inhibitor	186	-0.69 (0.95)	81/186	187	-0.87 ^c	1/191
		Placebo	175	0.13 (0.93)	29/175	176	-0.92 ^c	1/179
Ferrannini, ¹¹ 2009	52	DPP-4 inhibitor	1118	-0.44 (0.67)	605/1118	1118	-0.23 (3.68)	23/1389
		Sulfonylurea	1072	-0.53 (0.65)	595/1072	1072	1.56 (3.93)	224/1383
Goodman, ¹² 2009	24	DPP-4 inhibitor	119	-0.66 (1.2)	NR	119	-0.19 ^c	1/125
		Placebo	117	0.17 (1.19)	NR	117	-0.69 ^c	0/122
Nauck, ¹³ 2009	26	DPP-4 inhibitor	210	-0.6 (1.45)	92/210		-0.3 (0.33) ^d	0/210
		Placebo	104	-0.1 (1.02)	19/104			3/104
Nauck, ¹⁴ 2009	26	GLP-1 analog	242	-1.0 (1.56)	103/242	242	-2.8 (0.2)	7/242
		Sulfonylurea	242	-1.0 (1.56)	88/242	242	1.0 (0.2)	41/242
		Placebo	121	0.1 (1.1)	13/121	121	-1.5 (0.3)	4/121

(continued)

Table 1. Outcomes Reported by RCTs Evaluating Noninsulin Antidiabetic Drugs Added to Metformin in Patients With Type 2 Diabetes (continued)

Source	Follow-up, wk	Group	Change in HbA _{1c}		Achieved HbA _{1c} Goal <7% ^b	Change in Weight		Overall Hypoglycemia ^b
			No. ^a	Mean (SD), %		No. ^a	Mean (SD), kg	
Bolli, ^{15,16} 2008	52	DPP-4 inhibitor	295	-0.6 (1.14)	NR	295	0.2 (3.44)	1/295
		Thiazolidinedione	281	-0.6 (1.07)	NR	281	2.6 (5.03)	0/295
Hamann, ¹⁷ 2008	52	Thiazolidinedione	285	-0.78 (1.01)	NR	294	2.7 (5.14)	18/294
		Sulfonylurea	288	-0.86 (1.02)	NR	301	1.6 (5.20)	90/301
Khanolkar, ¹⁸ 2008	24	Thiazolidinedione	25	-1.19 (0.55)	NR	NR	NR	NR
		Sulfonylurea	25	-1.00 (0.67)	NR	NR	NR	NR
Raz, ¹⁹ 2008	30	DPP-4 inhibitor	95	-1 (1.49)	21/95	96	-0.5 ^c	1/96
		Placebo	92	0 (1.22)	3/92	94	-0.5 ^c	0/94
Scott, ²⁰ 2008	18	DPP-4 inhibitor	91	-0.73 (0.66)	50/91	94	-0.4 (1.98)	1/94
		Thiazolidinedione	87	-0.79 (0.64)	55/87	87	1.5 (2.14)	1/87
		Placebo	88	-0.22 (0.67)	33/88	91	-0.8 (1.95)	2/91
Ahrén, ^{21,22} 2007	52	DPP-4 inhibitor	42	-1.1 (0.2) ^d	18/42	42	-0.2 (0.47) ^e	0/42
		Placebo	29		3/29	21	-0.2 (0.58) ^e	0/29
Bosi, ²³ 2007	24	DPP-4 inhibitor	143	-0.9 (1.2)	NR	143	0.2 (3.59)	1/143
		Placebo	130	0.2 (1.14)	NR	130	1.0 (3.42)	1/130
Nauck, ²⁴ 2007	52	DPP-4 inhibitor	382	-0.64 (0.72)	240/382		-2.5 (0.28) ^d	29/588
		Sulfonylurea	411	-0.66 (0.78)	242/411			187/584
Charbonnel, ²⁵ 2006	24	DPP-4 inhibitor	453	-0.67 (1.09)	213/453	464	0.6 to 0.7 ^c	6/464
		Placebo	224	-0.02 (0.95)	41/224	237	0.6 to 0.7 ^c	5/237
Garber, ²⁶ 2006	24	Thiazolidinedione		-0.4 (0.12) ^d	91/153		-1.5 (0.45) ^d	2/155
		Sulfonylurea			71/152			60/159
Ristic, ^{27,28} 2006	52	Glinide	110	0.13 (0.15) ^d	44/110	110	0.42 ^c	19/112
		Sulfonylurea	99		47/99	99	0.91 ^c	16/101
DeFronzo, ²⁹ 2005	30	GLP-1 analog	113	-0.8 (1.06)	NR	113	-2.8 (5.32)	6/113
		Placebo	113	0.1 (1.06)	NR	113	-0.3 (3.19)	6/113
Feinglos, ³⁰ 2005	16	Sulfonylurea	61	-0.65 (0.78)	42/61	61	0.4 ^c	9/61
		Placebo	61	-0.18 (0.78)	17/61	61	-1.7 ^c	2/61
Matthews, ³¹ 2005	52	Thiazolidinedione		0.02 (0.09) ^d	NR	317	1.5 ^c	4/317
		Sulfonylurea			NR	313	1.4 ^c	35/313
Gómez-Perez, ³² 2002	26	Thiazolidinedione	36	-1.2 (1.84)	NR	NR	NR	NR
		Placebo	34	0.3 (1.49)	NR	NR	NR	NR
Marre, ³³ 2002	24	Glinide		-0.51 (0.12) ^d	NR	160	1.0 (2.53)	5/160
		Placebo			NR	152	0.1 (2.47)	1/152
Charpentier, ³⁴ 2001	20	Sulfonylurea	147	-0.74 (0.97)	NR	147	0.60 (2.86)	22/147
		Placebo	75	0.07 (1.21)	NR	75	-0.74 (2.58)	11/75
Van Gaal, ³⁵ 2001	32	AGI	76	-0.21 (1.13)	NR	76	-2.5 (3.8)	0/78
		Placebo	75	0.22 (1.17)	NR	75	-0.7 (2.5)	0/75
Fonseca, ³⁶ 2000	26	Thiazolidinedione		-1.2 (0.36) ^d	NR	110	1.9 ^c	5/113
		Placebo			NR	113	-1.2 ^c	2/116
Halimi, ³⁷ 2000	26	AGI	59	-0.7 (1.2)	NR	NR	NR	NR
		Placebo	70	0.2 (1.3)	NR	NR	NR	NR
Moses, ^{38,39} 1999	12	Glinide	27	-1.41 (1.20)	16/27	27	2.41 (2.6)	9/27
		Placebo	27	-0.33 (1.25)	5/27	27	-0.86 (2.65)	0/27
Rosenstock, ⁴⁰ 1998	24	AGI	73	-0.57 ^c	NR	74	-0.98 ^c	1/74
		Placebo	74	0.08 ^c	NR	74	-0.88 ^c	2/74

Abbreviations: AGI, α -glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NR, not reported; RCTs, randomized controlled trials.

^aMay not add up to total sample size due to attrition.

^bReported as No./total No.

^cReported without measures of variance; could not be meta-analyzed.

^dDifference between groups (referent given), given as mean (SE).

^eData provided by author via personal communication.

decreases in HbA_{1c} with sulfonylurea, glinide, thiazolidinedione, and DPP-4 inhibitor treatment compared with placebo (TABLE 3). In patients with baseline HbA_{1c} of 8% or more, there was also an association with greater decreases in HbA_{1c} with sulfonylurea, glinide, thiazolidinedione, AGI, DPP-4 inhibitor, and GLP-1 analog treatment compared with placebo. When evaluating the subgroup of studies in mixed-treatment comparison lasting 12 to 24 weeks, an association was found with greater decreases in HbA_{1c} with sulfonylurea, glinide, thiazolidinedione, and DPP-4 inhibitor treatment compared with placebo. In studies lasting more than 24 weeks in duration, there was also an association with greater HbA_{1c} reductions with sulfonylurea, glinide,

thiazolidinedione, AGI, DPP-4 inhibitor, and GLP-1 analog treatment compared with placebo. All of the above-mentioned subgroup analyses provided results consistent with our base case analysis. With sensitivity analysis, there was no significant change from results reported above when studies with a Jadad score of less than 3 were excluded from the analysis.

Body Weight

Sulfonylurea, glinide, and thiazolidinedione treatments were associated with increases in body weight compared with placebo in mixed-treatment comparison, with gains in body weight of 2.06 kg (95% CrI, 1.15-2.96 kg), 1.77 kg (95% CrI, 0.46-3.28 kg), and 2.08 kg (95% CrI, 0.98-3.17 kg), respectively

(eFigure 4 and eFigure 6). There was no weight change with AGIs (WMD, -1.80 kg; 95% CrI, -3.79 to 0.21 kg) or DPP-4 inhibitors (WMD, -0.14 kg; 95% CrI, -0.94 to 0.63 kg). The GLP-1 analogs were associated with significant weight loss (WMD, -1.74 kg; 95% CrI, -3.11 to -0.48 kg). Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (27 and 29, respectively). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 4).

Hypoglycemia

In mixed-treatment comparison meta-analysis, sulfonylurea (RR, 4.57; 95% CrI, 2.11-11.45) and glinide (RR, 7.50;

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

Group vs Placebo	% Change in HbA _{1c}		HbA _{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)
All drugs	20	-0.79 (-0.90 to -0.68) ^a	10	2.56 (1.99 to 3.28) ^b	12	0.14 (-1.37 to 1.65) ^a	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	-0.79 (-1.15 to -0.43) ^a	1	3.38 (2.02 to 5.83)	2	1.99 (0.86 to 3.12)	3	2.63 (0.76 to 9.13) ^a
Glinides	2	-0.71 (-1.24 to -0.18)	1	3.20 (1.47 to 7.58)	2	0.91 (0.35 to 1.46)	2	7.92 (1.45 to 43.21)
Thiazolidinediones	3	-1.00 (-1.62 to -0.38) ^b	1	1.69 (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	-0.65 (-1.11 to -0.19)	0	NA	1	-1.80 (-2.83 to -0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	-0.79 (-0.94 to -0.63) ^b	6	2.44 (1.78 to 3.33) ^b	4	-0.09 (-0.47 to 0.30) ^b	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	-0.99 (-1.19 to -0.78)	1	3.96 (2.37 to 6.79)	2	-1.76 (-2.90 to -0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.
^a*P* ≥ 75%.
^b*P* = 50%-75%.

Table 3. Results of Sensitivity and Subgroup Mixed-Treatment Comparison Meta-analysis of Change in HbA_{1c} Presented as WMD

Group vs Placebo	Relative Risk (95% CI)					
	Base Case (n = 26)	Baseline HbA _{1c}		Study Duration, wk		Jadad Score ≥ 3 (n = 25)
		<8% (n = 9)	≥8% (n = 16)	12-24 (n = 11)	>24 (n = 15)	
Sulfonylureas	-0.79 (-0.97 to -0.62)	-0.57 (-0.75 to -0.39)	-0.97 (-1.35 to -0.62)	-0.53 (-0.88 to -0.20)	-0.99 (-1.26 to -0.78)	-0.80 (-0.99 to -0.62)
Glinides	-0.65 (-0.97 to -0.36)	-0.44 (-0.85 to -0.04)	-0.65 (-1.10 to -0.26)	-0.65 (-1.15 to -0.24)	-0.86 (-1.36 to -0.42)	-0.66 (-0.99 to -0.35)
Thiazolidinediones	-0.85 (-1.08 to -0.66)	-0.62 (-0.88 to -0.39)	-1.02 (-1.39 to -0.69)	-0.75 (-1.14 to -0.24)	-0.95 (-1.27 to -0.73)	-0.88 (-1.14 to -0.66)
AGIs	-0.64 (-1.03 to -0.26)	NR	-0.65 (-1.07 to -0.24)	NR	-0.63 (-0.98 to -0.30)	-0.64 (-1.04 to -0.25)
DPP-4 inhibitors	-0.78 (-0.93 to -0.64)	-0.51 (-0.69 to -0.34)	-0.89 (-1.11 to -0.68)	-0.76 (-1.02 to -0.53)	-0.90 (-1.13 to -0.71)	-0.77 (-0.94 to -0.62)
GLP-1 analogs	-0.97 (-1.30 to -0.65)	NR	-0.99 (-1.36 to -0.63)	NR	-0.98 (-1.27 to -0.42)	-0.97 (-1.32 to -0.64)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NR, not reported; WMD, weighted mean difference.

95% CrI, 2.12-41.52) treatments were associated with increased risk of hypoglycemia compared with placebo (eFigure 5 and eFigure 6). Thiazolidinediones (RR, 0.56; 95% CrI, 0.19-1.69), AGIs (RR, 0.42; 95% CrI, 0.01-9.00), DPP-4 inhibitors (RR, 0.63; 95% CrI, 0.26-1.71), and GLP-1 analogs (RR, 0.89; 95% CrI, 0.22-3.96) were not associated with increased risk of hypoglycemia compared with placebo. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (50 and 50, respectively). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 5).

COMMENT

The ADA recommends drug therapy for treatment of type 2 DM based on the drug's ability to reduce hyperglycemia.¹ The ADA recommends that patients inadequately treated with metformin monotherapy (and lifestyle modification) should be initiated on either sulfonylureas or insulin.¹ Pioglitazone and the GLP-1 analog exenatide may also be selected and are listed as tier 2 drugs. However, the remaining drug classes (glinides, AGIs, and DPP-4 inhibitors) get only cursory mention due to the limited data supporting their efficacy.¹ Through conducting this mixed-treatment comparison and traditional meta-analysis, we determined the comparative efficacy (comparisons resulting from direct and indirect evidence) of different classes of noninsulin antidiabetic drugs. Traditional meta-analysis revealed HbA_{1c} reductions ranging between 0.62% and 1.00% in patients treated with various adjunctive drugs (added to inadequate, stable metformin) vs placebo. Patients treated with each adjunctive drug also had an increased RR of achieving an HbA_{1c} goal of less than 7% (RR range, 1.69-3.96) compared with placebo.

Our change in HbA_{1c} results were similar to a previous meta-analysis evaluating antidiabetic drug additions to metformin, in which HbA_{1c} reduc-

tions ranged between 0.42% and 0.85% vs placebo.³ The previous meta-analysis evaluated trials of sulfonylureas, glinides, thiazolidinediones, AGIs, and GLP-1 analogs, but not DPP-4 inhibitors.³ Furthermore, the meta-analysis by Monami et al³ did not use methods for incorporating indirect comparisons, and therefore was unable to assess the comparative efficacy of drugs. Our mixed-treatment comparison meta-analysis demonstrated that the different classes of drugs provided similar reductions in HbA_{1c} (range, 0.64%-0.97%) compared with placebo. The US Food and Drug Administration considers a margin of 0.4% to be the upper margin of noninferiority between drugs.⁴¹ Despite this, the ADA guidelines do not suggest that these drugs have similar glucose-lowering ability. The rate of HbA_{1c} goal attainment was also similar among classes of drugs (RR range, 2.25-3.20) using mixed-treatment comparison meta-analysis, with no statistically significant differences between noninsulin antidiabetic drugs.

In addition to demonstrating comparative efficacy of antidiabetic drugs, our meta-analysis also evaluated their associations with hypoglycemia and weight gain. In patients with type 2 DM, many are obese or overweight and have other comorbidities that can be affected by body weight.⁴² Potential increases in body weight due to antidiabetic drugs may negatively influence patient health by increasing the risk of cardiovascular disease⁴³ and should be a consideration when selecting drug therapy. Our mixed-treatment comparison meta-analysis demonstrated that glinides, sulfonylureas, and thiazolidinediones were associated with weight gain ranging between 1.77 kg and 2.08 kg compared with placebo. Glinides and sulfonylureas likely promote weight gain by increasing insulin secretion. Thiazolidinediones likely promote weight gain by increasing fluid retention.^{44,45} Glucagon-like peptide-1 analogs, AGIs, and DPP-4 inhibitors resulted in weight loss or no change in weight. Compared with sul-

fonylureas and thiazolidinediones, GLP-1 analogs were associated with an approximately 4-kg difference in weight, which in some patients may be close to the clinically relevant weight reduction value of 5% typically associated with decreased insulin resistance and improvements in serum lipids and blood pressure.⁴² Glucagon-like peptide-1 analogs may promote weight loss by increasing satiety and prolonging gastric emptying time.⁴⁶ α -Glucosidase inhibitors likely promote weight loss by decreased caloric absorption and as a result of gastrointestinal adverse effects.¹

The ADA guidelines emphasize the prevention of hypoglycemia as critical to the treatment strategy in type 2 DM.⁴² Therefore, considering a drug's hypoglycemic rate is warranted when selecting a drug. Although mild hypoglycemia produces bothersome symptoms, excessive decrease in blood glucose is associated with complications, including coma, cardiac arrhythmias, or myocardial ischemia.⁴⁷ Of the studies that reported hypoglycemia, patients receiving sulfonylureas or glinides experienced higher rates of hypoglycemia than placebo (RR range, 4.57-7.50). This increased risk is likely related to the increase in insulin release, which may occur independent of the presence of a glucose load.⁴⁸ The remaining drugs did not exhibit statistically significant differences in hypoglycemia risk compared with placebo.

In addition to the efficacy and safety aspects evaluated by this meta-analysis, considerations of contraindications (eg, heart failure, renal dysfunction), other adverse effects (eg, bone fracture, pancreatitis, or cardiovascular, gastrointestinal, and renal dysfunction), other therapeutic benefits (eg, pleiotropic effects), or cost may guide selection of therapy. Due to the limited reporting of these outcomes in RCTs, these were not included in our traditional or mixed-treatment comparison meta-analyses. Although DPP-4 inhibitors and GLP-1 analogs are associated with no change in weight or weight loss, they

are not available as generic products. Monthly costs for sitagliptin or exenatide range between US \$200 and \$250, but sulfonylureas may have monthly costs as low as \$5.⁴⁹

Our meta-analysis had limitations. Limitations typically observed in traditional meta-analysis, such as variations in treatment regimens or populations (heterogeneity), also apply to mixed-treatment comparison meta-analysis. Although estimates from the mixed-treatment comparison meta-analysis cannot simply be assumed accurate, we believe the reliability and robustness of our results are supported by (1) well-defined and strict inclusion and exclusion criteria, (2) observed goodness of model fit, (3) qualitative assessment demonstrating strong coherence, and (4) similarity of conclusions in subgroup and sensitivity analysis. Although many trials reported changes in body weight, data from some trials could not be meta-analyzed because measures of variance (SD, SE, or 95% CI) were not reported.† The underreporting of weight outcomes in these trials may reflect an underappreciation of the effect of treatment on body weight by investigators. Associations of weight gain or loss on serum lipids or blood pressure could not be assessed in our meta-analysis because these end points were not reported. Future studies should report these end points. We could not assess the effect of AGIs on attainment of an HbA_{1c} goal because trials evaluating AGIs did not report this end point. Therefore, we are unable to provide conclusions about the ability of AGIs to reach HbA_{1c} goal. Another limitation of our meta-analysis is that the duration of type 2 DM in patients in the studies ranged between 4.6 and 10.7 years, which may influence the efficacy of certain classes of drugs. In particular, sulfonylureas may have decreased efficacy in patients who have had DM for at least 6 years, because of pancreatic β -cell decline that goes along with the disease progression.⁵⁰ Addi-

tionally, the duration of prior metformin use may influence responsiveness to additional antidiabetic drugs, but this was not assessed due to the underreporting of this patient characteristic. Although the duration of prior metformin treatment may differ between trials, the use of randomization would likely have attenuated intrastudy variation.

In conclusion, noninsulin antidiabetic drugs when combined with metformin lowered HbA_{1c} to a similar degree; however, these drugs did not perform similarly in terms of body weight change and rates of hypoglycemia. These factors and other considerations should be taken into account when selecting a second-line treatment to add to stable, maximum metformin therapy.

Author Contributions: Drs Phung and Coleman 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.

Study concept and design: Phung, Coleman.

Acquisition of data: Phung, Scholle, Talwar, Coleman. **Analysis and interpretation of data:** Phung, Scholle, Coleman.

Drafting of the manuscript: Phung, Scholle, Talwar. **Critical revision of the manuscript for important intellectual content:** Phung, Scholle, Coleman.

Statistical analysis: Phung, Scholle.

Obtained funding: Phung, Coleman.

Administrative, technical, or material support: Phung, Scholle, Talwar, Coleman.

Study supervision: Coleman.

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