The Effect of Oral Antidiabetic Agents on A1C Levels

A systematic review and meta-analysis

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OBJECTIVE — Previous reviews of the effect of oral antidiabetic (OAD) agents on A1C levels summarized studies with varying designs and methodological approaches. Using predetermined methodological criteria, we evaluated the effect of OAD agents on A1C levels.

RESEARCH DESIGN AND METHODS — The Excerpta Medica (EMBASE), the Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Cochrane Central Register of Controlled Trials databases were searched from 1980 through May 2008. Reference lists from systematic reviews, meta-analyses, and clinical practice guidelines were also reviewed. Two evaluators independently selected and reviewed eligible studies.

RESULTS — A total of 61 trials reporting 103 comparisons met the selection criteria, which included 26,367 study participants, 15,760 randomized to an intervention drug(s), and 10,607 randomized to placebo. Most OAD agents lowered A1C levels by 0.5−1.25%, whereas thiazolidinediones and sulfonylureas lowered A1C levels by ~1.0–1.25%. By meta-regression, a 1% higher baseline A1C level predicted a 0.5 (95% CI 0.1–0.9) greater reduction in A1C levels after 6 months of OAD agent therapy. No clear effect of diabetes duration on the change in A1C with therapy was noted.

CONCLUSIONS — The benefit of initiating an OAD agent is most apparent within the first 4 to 6 months, with A1C levels unlikely to fall more than 1.5% on average. Pretreated A1C levels have a modest effect on the fall of A1C levels in response to treatment.

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Type 2 diabetes is a chronic, progressive disease that requires ongoing attention to lifestyle and pharmacotherapy to achieve and maintain optimal glucose control (1). Declining β-cell function and increasing insulin resistance over time lead to deteriorating glycemic control and the need for increasingly intense pharmacotherapy (1). Glycemic control is achieved by lifestyle and pharmacotherapy that targets fasting and postprandial glucose levels, as well as A1C levels—a measurement that reflects both fasting and postprandial glucose concentrations over a 3-month period (2).

Summaries of previous studies of oral antidiabetic drugs (OADs) suggest that they reduce A1C levels by 0.5–1.5% (2). However, this estimated drop in A1C was based on summaries of studies with varying designs, which may have led to over- or underestimates of the true effect of OADs. These summaries included studies with varying completeness of follow-up for both treatment and placebo groups, use of placebo control subjects, sample sizes, and durations of follow-up (3–6). We therefore completed a systematic review and meta-analysis of only those studies that met predetermined methodological criteria to estimate the effect of OADs on A1C levels.

RESEARCH DESIGN AND METHODS

Search strategy

We searched all relevant biomedical databases, including the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica (EMBASE), and the Cochrane Central Register of Controlled Trials. In consultation with a medical librarian, we developed a search strategy based on an analysis of medical subject headings, terms, and key text words from January 1980 to the present. A start date of January 1980 was intentionally chosen because A1C assays were becoming routinely available in the early 1980s (7). We combined terms for randomized controlled trials, placebo controlled trials, type 2 diabetes, oral hypoglycemics, OAD agents, and the classes of OADs including α-glucosidase inhibitors (acarbose and miglitol), biguanides (metformin), meglitinides (repaglinide and nateglinide), sulfonlyureas (glyburide, glimepiride, glipizide, glucotrol XL, gliclazide, and gliclazide MR), thiazolidinediones (TZDs) (rosiglitazone and pioglitazone), and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin and vildagliptin) (2). Reference lists from relevant meta-analyses, systematic reviews, and clinical guidelines were also examined. Online Appendix Fig. 1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1727) shows the search and selection process.

Study selection

All citations retrieved were reviewed against predetermined eligibility criteria. To be included, studies had to written in English, in a peer-reviewed journal between January 1980 and May 2008, and meet the following criteria: *1*) be a randomized, double-blind, placebo-controlled trial; *2*) report data on nonpregnant participants aged 18 and older with type 2 diabetes; *3*) report the differ-

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ential effect of the addition of an OAD versus placebo on the A1C level; *4*) report the effect of a single OAD versus placebo in subjects who were either drug naïve or on background therapy with an OAD and/or insulin; *5*) include at least 50 subjects in each arm; and *6*) report the effect of therapy on the A1C level in at least 70% of the randomized participants after a minimum of 12 weeks in every arm of the study (placebo and treatment arms). Studies were excluded if: *1*) they reported data on subjects who did not have type 2 diabetes; *2*) they reported data from first-generation sulfonylurea drugs or OADs withdrawn for safety reasons in any country; *3*) the intervention included the initiation of two OAD agents at the same time; or *4*) there was no statement that informed consent was obtained.

Data extraction

Two investigators (D.S. and K.N.) independently reviewed the titles, abstracts, and full articles for inclusion by using standardized forms. Discrepancies in eligibility were discussed between reviewers until agreement was achieved. Data abstraction was independently completed by two authors (D.S. and K.N.) and compared for accuracy. Items abstracted pertained to study characteristics, patient characteristics, and outcome results. As the main objective of this review and meta-analysis was to determine the effectiveness of OADs on A1C levels, rates of adverse events and hypoglycemia were not considered. The complete list of data abstracted is described in Online Appendix Table 1. A1C levels that were abstracted were those derived from any randomized subject who had an A1C level done within any given time interval. Unadjusted mean differences in A1C levels were collected. Authors were also contacted for further clarification regarding follow-up data at various time intervals and A1C values.

Statistical analysis

Data were categorized in the following time intervals after randomization: 12; 13–18; 19–24; 25–39; 40–47; 48–55; and 56–104 weeks. The mean difference between baseline to follow-up A1C levels at all available time intervals as well as measures of dispersion for placebo and treatment arms were recorded. If mean differences were not reported, a difference in means was calculated from the reported mean baseline and end point A1C values. A1C levels were abstracted from the text or tables, read from graphs, or computed. When more than one method for reporting the A1C level was used, the level reported in the text or table was used. When only the proportional mean decrease in A1C was provided for placebo and treatment arms, an end of study A1C level was calculated. All measures of dispersion were converted to SDs. When SDs were not reported, estimated baseline and final SDs were derived from data from other studies at the same time interval.

When more than one comparison arm was available for a specific drug and dose, a meta-analysis was completed at the reported time interval. As the focus of this review was on the glucose effect of different classes of drugs and not individual drugs, the results of different drugs and doses from the same class were meta-analyzed to yield an overall estimate. Cochran Q test and I-squared statistics were calculated for heterogeneity. If there was heterogeneity, pooled effects were calculated using a random-effects model (8).

A meta-regression analysis was also completed at each available time interval where there was sufficient data to assess the effect of baseline A1C and diabetes duration on the fall of A1C with OAD therapy. For this equation, the dependent variable was change in A1C, and the independent variables included: *1*) drug class; *2*) dose; *3*) diabetes duration; and *4*) baseline A1C. The dose variable in the regression equation was treated categorically with the starting dose coded as the baseline amount, and each doubling of a drug dose was a single increment increase. Agreement kappa statistics for each state of eligibility assessment were calculated using PC-Agree (McMaster University, Hamilton, Ontario, Canada) software. All statistical analyses were done using STATA statistical software (version 10.0) (StataCorp, College Station, TX).

RESULTS

Study and patient characteristics

A total of 61 studies comprising 103 different comparisons of OADs met the inclusion criteria. Thirty (49%) were found in EMBASE (Online Appendix references 1–30); 21 (34%) were found in the Cochrane Central Register of Controlled Trials (Online Appendix references 31–51); and 10 (16%) were found in MEDLINE (Online Appendix references 52–61). The studies were published between 1994 and 2008 with 79% of the studies published on or after 2000. Eligibility agreement was assessed between reviewers using a Cohen's κ coefficient and was 0.8 for title and abstract review and 0.8 for full article review. TZDs studies accounted for the greatest number of trials ($n = 27$), followed by DPP-4 inhibitors ($n = 26$), alpha glucosidase inhibitors ($n = 22$), biguanides ($n = 12$), meglitinides ($n = 10$), and sulfonylureas ($n = 6$). The duration of studies ranged from 12 to 156 weeks; 74% ranged from 12 to 24 weeks; 20% ranged from 25 to 52 weeks; and 6% exceeded 52 weeks. Funding sources for the trials included private for profit (73%); government, private for profit, and/or private not for profit (9%); and 18% of the studies did not report their funding source (Online Appendix Table 2).

The trials enrolled a combined total of 26,367 patients with 15,760 randomized to an intervention drug and 10,607 randomized to placebo. Background diabetes treatment in the studies included one or more OADs in 25 studies (41%); OAD plus insulin therapy in three studies (5%); and insulin only in six of the studies (10%). In 10 studies (16%), the subjects discontinued OAD therapy prior to randomization, and in 17 studies (28%), the subjects were drug naïve. Study subjects had a median age of 57 years (range 52–69 years of age) and were more likely to be male (median 57%, range 39–84). The median baseline A1C across the study populations was 8.3% (range 6.6–10%), and similar baseline A1C levels were seen across drug naïve patient groups (median 8.2, range 6.6–9.2), those on OAD(s) or discontinued OAD(s) (median 8.2, range 6.7–10) and patient populations using insulin (median 8.8, range 7.8–9.9). The median BMI was 30 (range 24–34) and the median duration of diabetes was 5 years (range 1.4–14 years of age) (Online Appendix Table 3).

OAD class effectiveness

Alpha glucosidase inhibitors. We identified 15 comparisons of acarbose and 6 comparisons of miglitol for which the effect on A1C for up to 2 years were reported (Fig. 1) (Fig. 2) (Online Appendix Figs. 2–7). All doses of both drugs, ranging from 75 to 900 mg per day, reduced A1C levels compared with placebo. Doses of 150 mg per day or higher achieved an A1C reduction of ~1% versus placebo with no evidence of an incremental effect

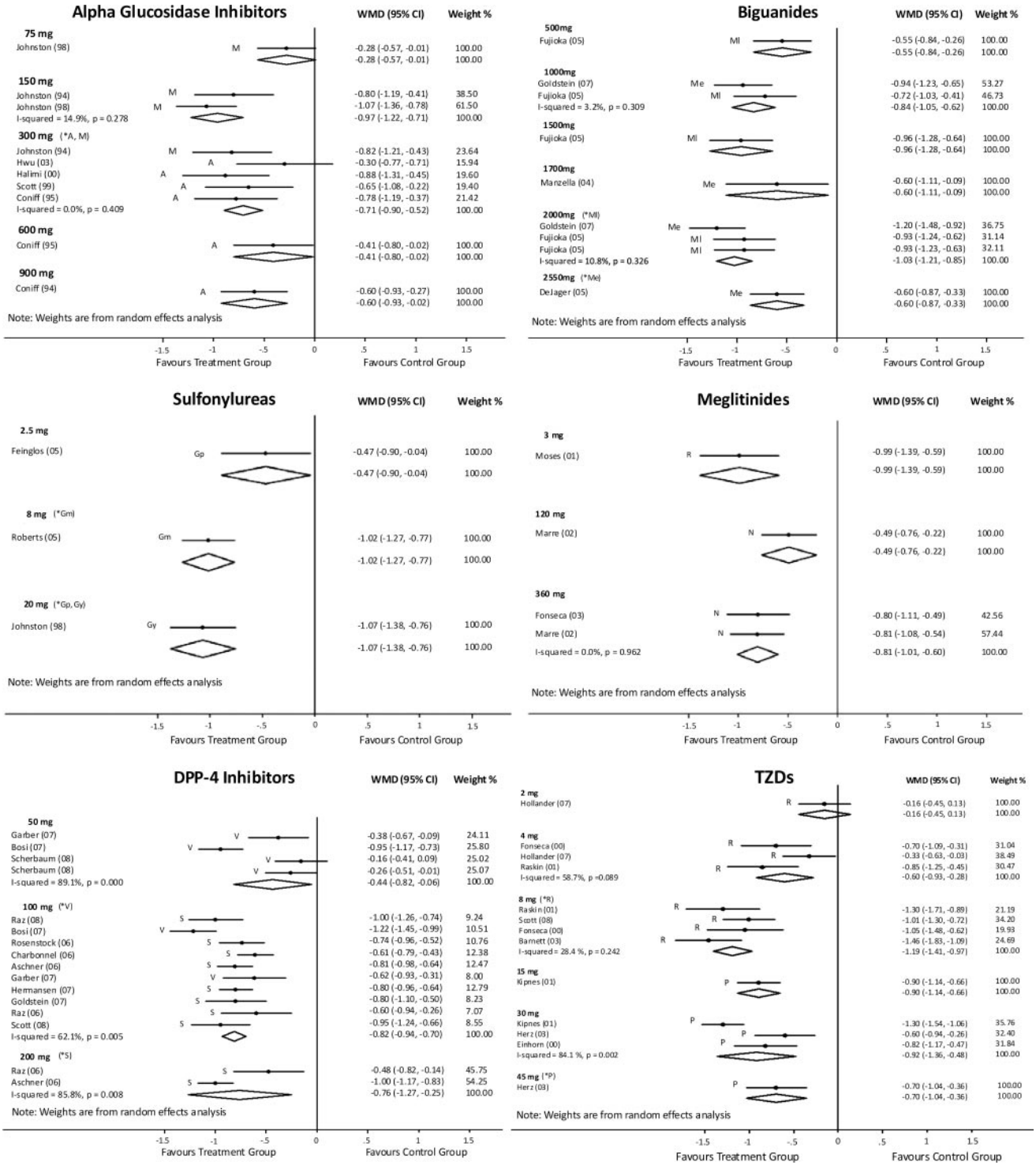

Figure 1—*Treatment effect by OAD class at 13–18 weeks. Each line represents a treatment effect (●) and 95% CIs (ends of the line). The diamond shape represents a meta-analyzed mean difference for a particular OAD class and dose. *Illustrates the generally accepted maximum daily dose. A, acarbose; Gm, glimepiride; Gp, glipizide; Gy, glyburide; M, miglitol; Me, metformin; Ml, metformin (long-acting); N, nateglinide; P, pioglitazone; R, rosiglitazone; Re, repaglinide; S, sitagliptin; V, vildagliptin.*

beyond that dose. The effect of these drugs persisted for up to 2 years (Fig. 2) (Online Appendix Figs. 2–7).

Biguanides. There were seven comparisons of metformin and five comparisons of long-acting metformin versus placebo that assessed doses ranging from 500 to 2,550 mg per day for up to 10 months (Figs. 1 and 2) (Online Appendix Figs. 3 and 4). Doses up to 1,500 mg per day reduced A1C levels by ~1% compared with placebo after 3 months of therapy. There was little evidence for additional reduction at higher doses, and the effect persisted for at least 10 months after treatment was begun.

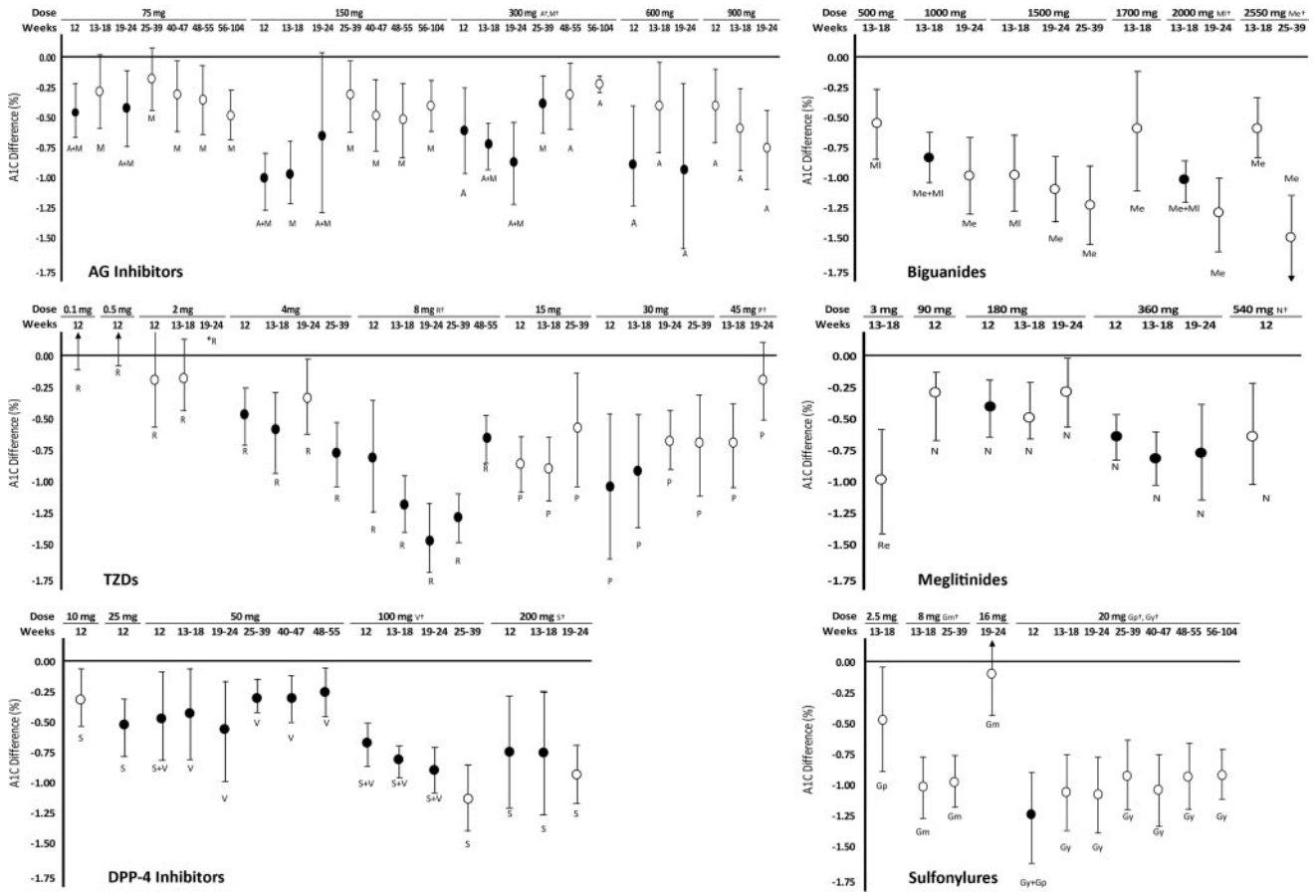

Figure 2—*Treatment effects on A1C by OAD class, dose, and time. Error bars represent 95% CIs.* ●*, represent pooled, weighted mean differences.* ○*, represent individual comparison treatment effects. *Treatment effect 1.1 (95% CI 0.8–1.4). †Illustrates the generally accepted maximum daily dose. A, acarbose; AG-α, glucosidase inhibitors; Gm, glimepiride; Gp, glipizide; Gy, glyburide; M, miglitol; Me, metformin; Ml, metformin (long-acting); N, nateglinide; P, pioglitazone; R, rosiglitazone; Re, repaglinide; S, sitagliptin; V, vildagliptin.*

DPP-4 inhibitors. A total of 19 comparisons of sitagliptin and 7 comparisons of vildagliptin were identified in which the effect on A1C for up to 1 year were reported (Figs. 1 and 2) (Online Appendix Figs. 2–6). All doses of both drugs, ranging from 10 to 200 mg per day, reduced A1C levels compared with placebo. Doses of 100 mg per day or higher achieved an A1C reduction of ~0.75% versus placebo with no evidence of an incremental effect beyond that dose.

Meglitinides. We found eight comparisons of nateglinide with doses ranging from 90 to 540 mg per day and one comparison of repaglinide at 3 mg per day versus placebo for up to 6 months in duration. Doses up to 360 mg per day reduced A1C levels by ~0.75% compared with placebo after 3 months of therapy. There was little evidence for additional reduction at higher doses (Figs. 1 and 2) (Online Appendix Figs. 2 and 3).

Sulfonylureas. Our search identified three comparisons of glipizide (doses ranging from 2.5 to 20 mg per day), two of glimepiride (doses ranging from 8 to 16 mg per day), and one of glyburide (20 mg per day) for which the effect on A1C for up to 2 years was reported (Figs. 1 and 2) (Online Appendix Figs. 2–7). As indicated in Fig. 2, doses ≥8 mg per day of glimepiride generally achieved an A1C reduction of ~1.25% versus placebo. The studies suggested that the effect of these drugs persisted for at least 2 years (Fig. 2) (Online Appendix Figs. 2–7).

TZDs. We identified 17 comparisons of rosiglitazone and 10 comparisons of pioglitazone for which the effect on A1C for up to 1 year were reported (Figs. 1 and 2) (Online Appendix Figs. 2–4, 6). One low-dose study of rosiglitazone assessing doses of 0.1, 0.5, and 2 mg per day did not show any effect on A1C levels. Daily doses of 4–8 mg of rosiglitazone and 15–45 mg of pioglitazone reduced A1C levels compared with placebo. Rosiglitazone at 8 mg per day achieved an A1C reduction of ~1.25% versus placebo, and pioglitazone at 30 mg per day achieved an A1C reduction of ~1% versus placebo (Fig. 2). The effect of these drugs persisted for at least 1 year in these studies (Fig. 2) (Online Appendix Figs. 2–4, 6).

The effect of baseline A1C and diabetes duration levels on the fall of A1C

After adjusting for drug class, dose, diabetes duration, and baseline A1C in the meta-regression analysis, the addition of an OAD led to a 0.2–0.5% greater decline for every 1% higher baseline A1C level. As noted in Table 1 (Table 1), this effect was statistically significant beyond 13 weeks. No consistent effect of diabetes duration on the change in A1C was noted. Insufficient data regarding diabetes duration precluded estimating the effect of diabetes duration and baseline A1C in studies of 40 or more weeks' duration. The effect of baseline A1C on the change in A1C with therapy could not be adjusted for changes

Table 1—*The effect of baseline A1C and diabetes duration on the fall in A1C with OAD therapy*

Follow-up time (weeks)	Comparisons (*n*)	Change in A1C (%) for every 1% higher baseline A1C (95% CI)*	Change in A1C (%) for every 1 year greater diabetes duration (95% CI)**
12	50	0.01 (−0.2 to 0.2)	−0.1 (−0.13 to −0.002)†
13–18	57	−0.2 (−0.4 to −0.05)‡	0.03 (−0.01 to −0.1)
19–24	47	−0.3 (−0.6 to −0.1)§	0.08 (0.01–0.15)¶
25–39	21	−0.5 (−0.9 to −0.1)¶	−0.03 (−0.1 to 0.1)

Estimates are derived from a meta-regression analysis that controlled for: *drug class, drug dose, and baseline A1C; **drug class, drug dose, baseline A1C, and duration of diabetes. †$P < 0.05$; ‡$P < 0.02$; §$P < 0.01$; ¶$P < 0.03$.

in the dose of insulin during the study as insulin doses were not always recorded.

CONCLUSIONS — This systematic review and meta-analysis of double-blind, randomized controlled trials that met predefined methodological criteria summarized treatment effects on A1C levels across OAD drug class, dose, and duration of therapy (Fig. 2). The greatest pooled treatment effect noted was with maximum doses of sulfonylureas after 12 weeks of therapy, followed by TZDs after 13–18 weeks of therapy. Across all OAD classes, an increase in dose yielded a further decrease in A1C initially with a maximum effect achieved by 3–6 months.

The meta-regression analysis also provided a numerical estimate of an effect that has been commented on by previous authors: higher baseline A1C levels are associated with greater declines in A1C with therapy (9). However, this effect was modest in most studies that were reviewed, such that after controlling for OAD drug class and dose, every 1% higher pretreatment A1C levels predicted a 0.5% greater fall of A1C levels after 6 months of therapy.

This review has several strengths. First, it was restricted to randomized controlled trials that met predetermined methodological criteria to minimize the potential for bias. Of note, the application of these criteria led to the exclusion of 150 out of 211 (71%) manuscripts that may otherwise have been included. Second, it entailed a comprehensive search for all currently used OAD classes for type 2 diabetes treatment. Third, the effect of OADs on A1C level was assessed at different time intervals, ranging from 12 weeks to 2 years. Finally, it focused on the effect of OAD class versus individual drugs and therefore may be relevant to new drugs from the same class.

This review has several limitations. First, most of the studies included participants with relatively newly diagnosed diabetes (median duration of diabetes of 5.2 years). As such, the review's findings may not be relevant to patients with a longer duration of diabetes or with diabetes-related complications. Second, relatively few studies were available for sulfonylureas ($n = 6$), meglitinides ($n = 10$), and biguanides ($n = 12$) thereby affecting the reliability of their respective quantitative estimates. Third, less than 30% of the reviewed papers reported the effect of therapy for periods greater than 24 weeks. Fourth, there is some statistical heterogeneity (ranging up to 90%) in the meta-analyzed results of the included studies, regardless of OAD class, drug, or dose. This heterogeneity may have been due to study differences in design, patient demographics and characteristics, duration of diabetes, and background drug therapy or confounding. Regardless of the cause, heterogeneity was managed by using a random-effects model for meta-analyses. Fifth, some of the summarized trials added oral agents to background therapy that included insulin. If investigators adjusted the dose of insulin during the trial, this may have affected the estimate of the effect of the OAD on the change in A1C. This could not be taken into consideration as insulin doses were not provided in the reports. Finally, it is possible that this review was influenced by publication bias given that studies with positive results are generally more likely to get published, resulting in an overestimate of the benefit of an OAD on A1C reduction.

In summary, the results of this systematic review and meta-analysis suggest that the initiation of an OAD in addition to current therapy yields an additional decrease in A1C level of ~1–1.25% with most of the treatment effect evident by 3–6 months of initiating OAD therapy. This effect was fairly consistent between OAD classes with sulfonylureas and TZDs having the greatest reduction in AIC. The meta-regression analysis numerically demonstrated a small effect of baseline A1C on the fall of A1C with OAD treatment. Further carefully conducted OAD trials are needed to account for *1*) combinations of OAD drug use and its impact on A1C levels; *2*) the effectiveness of long-term OAD use on A1C levels; and *3*) adverse and hypoglycemic events.

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No other potential conflicts of interest relevant to this article were reported.

All the authors of this manuscript 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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