REVIEW | Annals of Internal Medicine

Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus

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Background: As newer oral diabetes agents continue to emerge on the market, comparative evidence is urgently required to guide appropriate therapy.

Purpose: To summarize the English-language literature on the benefits and harms of oral agents (second-generation sulfonylureas, biguanides, thiazolidinediones, meglitinides, and α-glucosidase inhibitors) in the treatment of adults with type 2 diabetes mellitus.

Data Sources: The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched from inception through January 2006 for original articles and through November 2005 for systematic reviews. Unpublished U.S. Food and Drug Administration and industry data were also searched.

Study Selection: 216 controlled trials and cohort studies and 2 systematic reviews that addressed benefits and harms of oral diabetes drug classes available in the United States.

Data Extraction: Using standardized protocols, 2 reviewers serially abstracted data for each article.

Data Synthesis: Evidence from clinical trials was inconclusive on major clinical end points, such as cardiovascular mortality. Therefore, the review was limited mainly to studies of intermediate end points. Most oral agents (thiazolidinediones, metformin, and repaglinide) improved glycemic control to the same degree as sulfonylureas (absolute decrease in hemoglobin A_{1c} level of about 1 percentage point). Nateglinide and α-glucosidase inhibitors may have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. Thiazolidinediones were the only class that had a beneficial effect on high-density lipoprotein cholesterol levels (mean relative increase, 0.08 to 0.13 mmol/L [3 to 5 mg/dL]) but a harmful effect on low-density lipoprotein (LDL) cholesterol levels (mean relative increase, 0.26 mmol/L [10 mg/dL]) compared with other oral agents. Metformin decreased LDL cholesterol levels by about 0.26 mmol/L (10 mg/dL), whereas other oral agents had no obvious effects on LDL cholesterol levels. Most agents other than metformin increased body weight by 1 to 5 kg. Sulfonylureas and repaglinide were associated with greater risk for hypoglycemia, thiazolidinediones with greater risk for heart failure, and metformin with greater risk for gastrointestinal problems compared with other oral agents. Lactic acidosis was no more common in metformin recipients without comorbid conditions than in recipients of other oral diabetes agents.

Limitations: Data on major clinical end points were limited. Studies inconsistently reported adverse events other than hypoglycemia, and definitions of adverse events varied across studies. Some harms not assessed in trials or observational studies may have been overlooked.

Conclusions: Compared with newer, more expensive agents (thiazolidinediones, α-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control, lipids, and other intermediate end points. Large, long-term comparative studies are needed to determine the comparative effects of oral diabetes agents on hard clinical end points.

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The prevalence and morbidity associated with type 2 diabetes mellitus continue to increase in the United States and elsewhere (1, 2). Several studies of the treatment of type 2 diabetes suggest that improved glycemic control reduces microvascular risks (3–7). In contrast, the effects of treatment on macrovascular risk are more controversial (3, 4, 8, 9), and the comparative effects of oral diabetes agents on clinical outcomes are even less certain. As newer oral agents, such as thiazolidinediones and meglitinides, are increasingly marketed, clinicians and patients must decide whether they prefer these generally more costly medications over older agents, such as sulfonylureas and metformin.

Systematic reviews and meta-analyses of oral diabetes agents have attempted to fill this gap (10–19), but few have compared all agents with one another (18, 19). The few investigations that have compared all oral agents focused narrowly on individual outcomes, such as hemoglobin A_{1c} level (18) or serum lipid levels (19). No systematic review has summarized all available head-to-head comparisons with regard to the full range of intermediate end points (including hemoglobin A_{1c} level, lipid levels, and body weight) and other clinically important outcomes, such as adverse effects and macrovascular risks. Therefore, the Agency for Healthcare Research and Quality commissioned a systematic review to summarize the comparative

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benefits and harms of oral agents that are used to treat type 2 diabetes.

Methods

Data Sources and Selection

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to January 2006 for original articles. We also searched these databases until November 2005 for systematic reviews. We reviewed reference lists of related reviews and original data articles, hand-searched recent issues of 15 medical journals, invited experts to provide additional citations, reviewed selected medications from the U.S. Food and Drug Administration (FDA) Web site, and reviewed unpublished data from several pharmaceutical companies and public registries of clinical trials. Our search strategy for the bibliographic databases combined terms for type 2 diabetes and oral diabetes agents and was limited to English-language articles and studies in adults. The search for systematic reviews was similar but included terms for study design as well.

We selected studies that included original data on adults with type 2 diabetes and assessed benefits or harms of FDA-approved oral diabetes agents that were available in the United States as of January 2006. To facilitate head-to-head comparisons of drug classes, we included drugs not on the U.S. market if members of their class were in use and had not been banned (voglibose, gliclazide, and glibenclamide). We also included studies of combinations of therapies that are commonly used, such as combinations of metformin, second-generation sulfonylureas, and thiazolidinediones. We excluded studies that evaluated combinations of 3 oral diabetes agents, and we also excluded first-generation sulfonylureas, because few clinicians prescribe these medications.

We sought studies that reported on major clinical outcomes (for example, all-cause mortality, cardiovascular morbidity and mortality, and microvascular outcomes) or any of the following intermediate end points or adverse events: hemoglobin A_{1c} level, body weight, systolic and diastolic blood pressure, high-density lipoprotein (HDL) cholesterol level, low-density lipoprotein (LDL) cholesterol level, triglyceride level, hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated aminotransferase levels, liver failure, anemia, leukopenia, thrombocytopenia, allergic reactions requiring hospitalization or causing death, and other serious adverse events. For intermediate end points, we included only randomized, controlled trials, which were abundant. For major clinical end points and adverse events, we considered observational studies as well as trials, because fewer randomized trials assessed these end points. We excluded studies that followed patients for less than 3 months (the conventional threshold for determining effects on hemoglobin A_{1c}) or had fewer than 40 patients. **Figure 1** shows the search and selection process, and the full technical report (available at http://effectivehealthcare.ahrq.gov/repFiles/OralFullReport.pdf) provides a more detailed description of the study methods (20).

Data Extraction and Quality Assessment

One investigator used standardized forms to abstract data about study samples, interventions, designs, and outcomes, and a second investigator confirmed the abstracted data. Two investigators independently applied the Jadad scale to assess some aspects of the quality of randomized trials (21). We considered observational studies and nonrandomized trials to provide weaker evidence than randomized trials, and we did not use a standardized scoring system to assess their quality (22). We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group definitions to grade the overall strength of the evidence as high, moderate, low, very low, or insufficient (23).

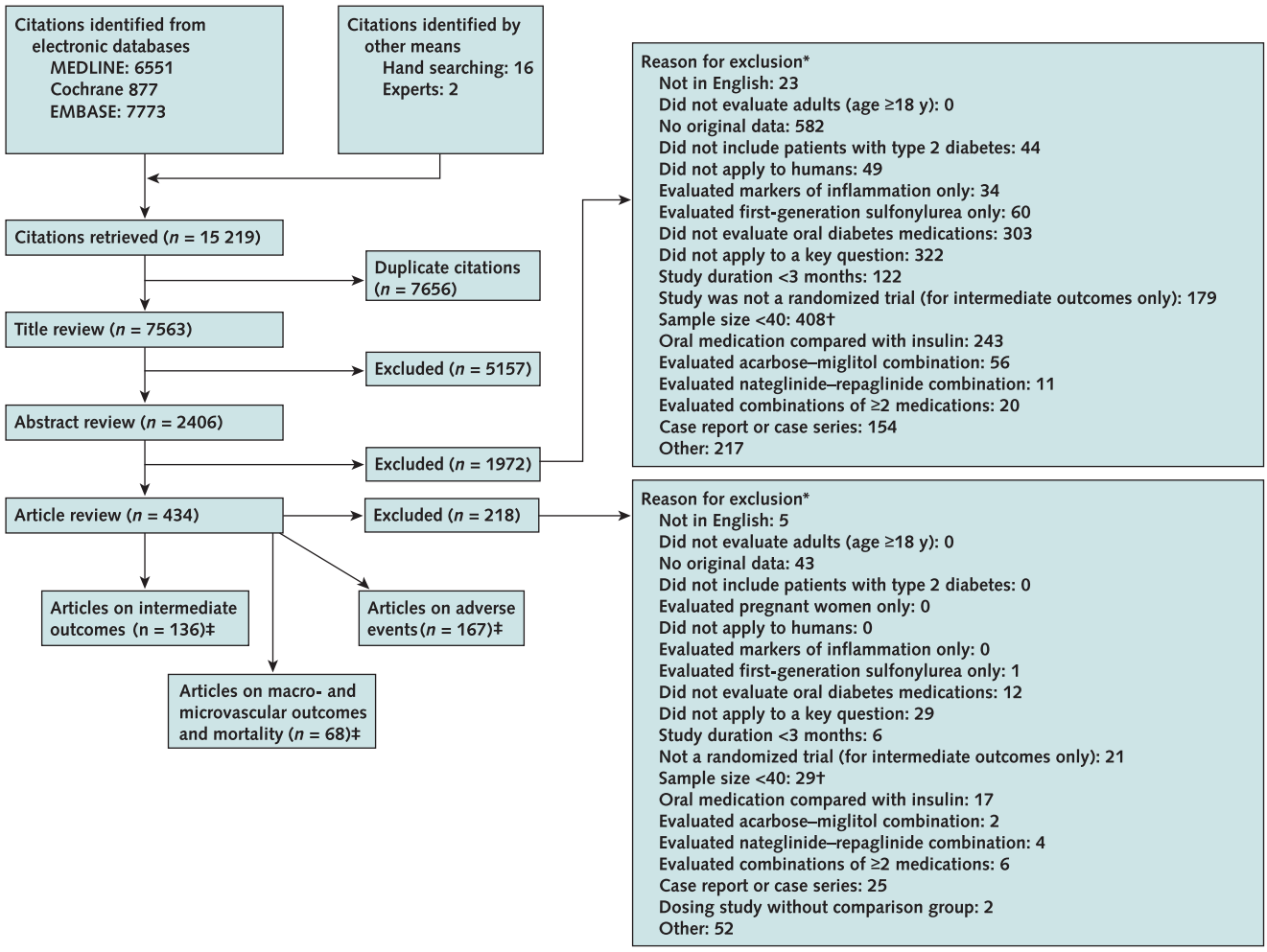
Data Synthesis and Analysis

We first performed a qualitative synthesis based on scientific rigor and type of end point. In general, we described the UKPDS (United Kingdom Prospective Diabetes Study) separately, because this large randomized, controlled trial differed from other trials in design, end points, and duration.

When data were sufficient (that is, obtained from at least 2 randomized, controlled trials) and studies were relatively homogeneous in sample characteristics, study duration, and drug dose, we conducted meta-analyses for the following intermediate outcomes and adverse effects: hemoglobin A_{1c} level, weight, systolic blood pressure, LDL cholesterol level, HDL cholesterol level, triglyceride level, and hypoglycemia. For trials with more than 1 dosing group, we chose the dose that was most comparable with other trials and most clinically relevant. We combined drugs into drug classes only when similar results were found across individual drugs. We could not perform formal meta-analyses for microvascular or macrovascular outcomes, mortality, and adverse events other than hypoglycemia because of methodological diversity among the trials or insufficient numbers of trials.

We used a random-effects model with the DerSimonian and Laird formula to derive pooled estimates (posttreatment weighted mean differences for intermediate outcomes and posttreatment absolute risk differences for adverse events) (24). We tested for heterogeneity among the trials by using a chi-square test with α set to 0.10 or less and an I^2 statistic greater than 50% (25). If heterogeneity was found, we conducted meta-regression analyses by using study-level characteristics of double-blinding, study duration, and dose ratio (calculated as the dose given in the study divided by the maximum approved dose of drug). The full report contains data on indirect comparisons, in which 2 interventions are compared through their relative effect against a common comparator (20). We tested for publication bias by using the tests of Begg and Mazumdar

Figure 1. **Study flow diagram.**



*Numbers add up to more than the number of abstracts or articles excluded because there may have been more than 1 reason for exclusion. †More than two thirds of the articles that were excluded for having fewer than 40 participants would have been excluded for other reasons as well. ‡The numbers of articles for intermediate outcomes, adverse events, microvascular and macrovascular outcomes, and mortality are not mutually exclusive.

(26) and Egger and colleagues (27). All statistical analyses were done by using STATA Intercooled, version 8.0 (Stata, College Station, Texas).

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and provided copyright release for this manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS

Comparative Effectiveness of Oral Diabetes Agents in Reducing the Risk for Microvascular and Macrovascular Outcomes and Death

We found no definitive evidence about the comparative effectiveness of oral diabetes agents on all-cause mortality, cardiovascular mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy (**Table 1**). For each head-to-head comparison on specific outcomes, the number of randomized trials (≤3 trials) and the absolute number of events were small (20). The few observational studies were limited in quantity, consistency, and adjustment for key confounders.

Since our review, 2 high-profile comparative randomized trials with about 4 years of follow-up have been published, providing data on cardiovascular outcomes (28, 29). In ADOPT (A Diabetes Outcome Progression Trial) (28), the incidence of cardiovascular events was lower with glyburide than with rosiglitazone or metformin (1.8%, 3.4%, and 3.2%, respectively; $P < 0.05$). This effect was mainly driven by fewer congestive heart failure events and a lower rate of nonfatal myocardial infarction events in the glyburide group. Loss to follow-up was high (40%) and was disproportionate among the groups and therefore may account for some differences among groups.

Table 1. **Evidence of the Comparative Effectiveness of Oral Diabetes Medications on Mortality, Microvascular and Macrovascular Outcomes, and Intermediate End Points***

Outcome	Level of Evidence†	Conclusions
All-cause mortality	Low to very low	It was unclear whether mortality differed when metformin plus a sulfonylurea was compared with sulfonylurea or metformin monotherapy or when metformin was compared with sulfonylureas.
	Very low	Data were insufficient to compare other oral diabetes medications.
Cardiovascular disease mortality	Low to very low	It was unclear whether cardiovascular mortality differed when metformin plus a sulfonylurea was compared with sulfonylurea or metformin monotherapy. It was unclear whether the effects on cardiovascular mortality differed between metformin and sulfonylureas.
	Very low	Data were insufficient to compare other oral diabetes medications.
Cardiovascular morbidity (nonfatal myocardial infarction and stroke)	Low to very low	There were too few studies to support conclusions about how cardiovascular morbidity differed between the medications, except that the risk for congestive heart failure is increased with thiazolidinediones compared with other oral agents.
Peripheral vascular disease	Low to very low	No evidence exists for a difference between oral diabetes medications in effects on peripheral vascular disease.
Microvascular outcomes (retinopathy, nephropathy, neuropathy)	Low to very low	Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.
HbA_{1c} level	Moderate to high	Most oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and metformin) produced similar absolute reductions in HbA_{1c} level (approximately 1%) compared with one another as monotherapy. Repaglinide produced similar reductions in HbA_{1c} level when compared directly with sulfonylureas. Combination therapies were better at reducing the HbA_{1c} level than was monotherapy by about 1% (absolute difference).
	Low	Repaglinide produced similar reductions in HbA_{1c} level when compared indirectly with thiazolidinediones and metformin. Indirect data and data from a few head-to-head trials showed that nateglinide and α-glucosidase inhibitors were less efficacious in reducing HbA_{1c} levels (approximately 0.5%–1% absolute difference).
Systolic and diastolic blood pressure	Moderate to low for most comparisons‡	Most oral diabetes medications (thiazolidinediones, metformin, and sulfonylureas) had similarly minimal effects on systolic and diastolic blood pressure (<5 mm Hg).
	Insufficient	Too few studies compared meglitinides with oral diabetes medications other than sulfonylureas to permit firm conclusions.
LDL cholesterol level	Moderate for most comparisons§	Thiazolidinedione monotherapy and rosiglitazone plus metformin or a sulfonylurea increased LDL cholesterol levels (approximately 0.26–0.31 mmol/L [10–12 mg/dL]) compared with metformin or second-generation sulfonylurea monotherapy, which generally decreased LDL cholesterol levels. Rosiglitazone increased LDL cholesterol levels more than pioglitazone (approximately 0.26–0.39 mmol/L [10–15 mg/dL]), according to indirect comparisons and a few head-to-head comparisons. Metformin decreased LDL cholesterol levels compared with second-generation sulfonylureas (approximately 10 mg/dL). Metformin plus a sulfonylurea decreased LDL cholesterol levels compared with second-generation sulfonylurea monotherapy (approximately 0.21 mmol/L [8 mg/dL]).
	Low	Metformin monotherapy compared with metformin plus a sulfonylurea had similar effects on LDL cholesterol levels. Second-generation sulfonylureas had similar effects on LDL cholesterol levels compared with repaglinide. α-Glucosidase inhibitors had similar effects on LDL cholesterol levels compared with second-generation sulfonylureas.
	Low to very low	Indirect comparisons of acarbose and metformin showed similar effects on LDL cholesterol levels. The one direct comparison favored acarbose at maximal doses over metformin at submaximal doses. According to 1 head-to-head trial and mainly indirect comparisons, rosiglitazone increased LDL cholesterol levels more than acarbose (approximately 0.26–0.39 mmol/L [10–15 mg/dL]).
	Insufficient	Too few studies compared meglitinides with other oral diabetes medications (other than sulfonylureas) to draw firm conclusions.
HDL cholesterol level	Moderate	Pioglitazone increased HDL cholesterol levels more than rosiglitazone, according to indirect and a few direct comparisons (approximately 0.03–0.08 mmol/L [1–3 mg/dL]).

Continued on following page

Table 1—**Continued**

Outcome	Level of Evidence†	Conclusions
HDL cholesterol level (continued)		Pioglitazone increased HDL cholesterol levels compared with metformin or second-generation sulfonylureas (approximately 0.08–0.13 mmol/L [3–5 mg/dL]).
	Moderate to low	The combination of rosiglitazone with metformin or a second-generation sulfonylurea increased HDL cholesterol levels slightly more than metformin or second-generation sulfonylureas alone (approximately 0.08 mmol/L [3 mg/dL]). Metformin, second-generation sulfonylureas, acarbose, and meglitinides had similarly minimal or no effect on HDL cholesterol levels. Combination therapy with metformin plus a second-generation sulfonylurea did not differ in effect on HDL cholesterol levels from monotherapy with either of the 2 classes.
Triglyceride level	Moderate	Indirect comparisons and a few head-to-head comparisons showed that pioglitazone decreased triglyceride levels (range, 0.17–0.59 mmol/L [15–52 mg/dL]) compared with rosiglitazone, which increased triglyceride levels (range, 0.07–0.15 mmol/L [6–13 mg/dL]).
	Moderate to low	Pioglitazone decreased triglyceride levels more than metformin (approximately 0.29 mmol/L [26 mg/dL]), and decreases were similar compared with sulfonylureas. However, the pooled estimate suggested a potential statistically nonsignificant difference of approximately 0.33 mmol/L (29 mg/dL) compared with sulfonylureas. Metformin decreased triglyceride levels more than second-generation sulfonylureas and more than metformin plus rosiglitazone (approximately 0.11 mmol/L [10 mg/dL]). Metformin plus a second-generation sulfonylurea decreased triglyceride levels more than sulfonylurea monotherapy (approximately 0.34 mmol/L [30 mg/dL]) and produced a statistically nonsignificant decrease in triglyceride levels compared with metformin monotherapy. Second-generation sulfonylureas had similar effects on triglyceride levels compared with repaglinide and acarbose.
	Low	Indirect comparisons and 1 direct comparison showed that pioglitazone decreased triglyceride levels more than acarbose (approximately 0.34 mmol/L [30 mg/dL]). Rosiglitazone increased triglyceride levels when compared indirectly with metformin and acarbose, yet had similar effects on triglyceride levels when compared directly with metformin.
	Low to very low	According to indirect and a few direct comparisons, metformin showed similar effects on triglyceride levels when compared with acarbose.
	Insufficient	Too few comparisons were available for nateglinide to draw conclusions.
Body weight	High to moderate	Thiazolidinediones, second-generation sulfonylureas, and combinations of metformin plus second-generation sulfonylureas consistently increased body weight by 1 to 5 kg when compared directly with metformin, which was weight-neutral in placebo-controlled trials.
	Moderate	Repaglinide had similar effects on body weight compared with second-generation sulfonylureas. There were too few comparisons of repaglinide with other oral diabetes medications to draw conclusions.
	Low	Thiazolidinediones and second-generation sulfonylureas caused similar weight gain (approximately 3 kg) when used as monotherapy or in combination therapy with other oral diabetes medications. Thiazolidinediones caused weight gain (approximately 3 kg) compared with acarbose and repaglinide, according to indirect comparisons of placebo-controlled trials and a few direct comparisons. Acarbose compared with sulfonylureas showed no statistically significant differences in weight, but there was a suggestion of differences between groups in the direct comparisons. The indirect comparisons showed that sulfonylureas were associated with weight gain compared with acarbose, which was weight-neutral. According to a few head-to-head comparisons and indirect comparisons, acarbose had similar weight effects compared with metformin.
	Insufficient	There were too few comparisons of nateglinide with other oral diabetes medication to evaluate its effect on weight.

*HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized, controlled trial.
† Evidence was rated as follows: high = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain; insufficient = not graded if too few comparisons (<3 studies) and not a key comparison of interest.
‡ Evidence was graded as very low for the following comparisons related to blood pressure effects: metformin versus metformin plus sulfonylurea, sulfonylurea versus sulfonylurea plus thiazolidinedione, meglitinides versus sulfonylureas, and α-glucosidase inhibitors versus all other oral diabetes medications.
§ Evidence was graded as moderate to low for rosiglitazone plus metformin and for second-generation sulfonylureas compared with monotherapy. The rest of the comparisons were graded as moderate.

The interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study reported that rosiglitazone plus metformin or a sulfonylurea compared with metformin plus a sulfonylurea had a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease (29). The hazard ratio was driven by more congestive heart failure in the rosiglitazone plus metformin or sulfonylurea group than in the control group of metformin plus sulfonylurea (absolute risk, 1.7% vs. 0.8%, respectively). In Kaplan–Meier curves, the risk for hospitalization or death from myocardial infarction was slightly lower in the control group than in the rosiglitazone group, but the difference was not statistically significant. A limitation of this interim analysis was the lack of power to detect differences, owing to fewer cardiovascular events than initially predicted.

Comparative Effectiveness of Oral Diabetes Agents in Improving Intermediate Outcomes

Summary of Evidence

The strength of evidence was moderate to high that most oral agents (thiazolidinediones, metformin, and repaglinide) improved glycemic control to the same degree as sulfonylureas (decrease in hemoglobin A_{1c} level, about 1 absolute percentage point). Nateglinide and α-glucosidase inhibitors may have slightly weaker effects on hemoglobin A_{1c} levels on the basis of indirect comparisons of placebo-controlled trials (low strength of evidence). The strength of evidence was moderate that, compared with most other oral agents, thiazolidinediones had a beneficial effect on HDL cholesterol levels (relative mean increase, 0.08 to 0.13 mmol/L [3 to 5 mg/dL]) but a harmful effect on LDL cholesterol levels (relative mean increase, 0.26 mmol/L [10 mg/dL]). Metformin decreased LDL cholesterol levels by about 0.26 mmol/L (10 mg/dL), whereas other oral agents had no obvious effect on LDL cholesterol levels. The strength of evidence was moderate that thiazolidinediones, second-generation sulfonylureas, and metformin had similarly minimal effects on systolic blood pressure. There was moderate evidence that most agents other than metformin increased body weight by about 1 to 5 kg. Metformin had no effect on body weight in placebo-controlled trials.

Table 1 shows evidence grades and a summary of the comparative conclusions. These studies applied primarily to patients with type 2 diabetes and no major comorbid conditions.

Characteristics and Quality of Studies of Intermediate Outcomes

The full report (20) provides a list of references and detailed evidence tables. We found 136 randomized trials that addressed intermediate outcomes and a systematic review on acarbose versus other oral diabetes agents (20). Study duration ranged from 12 weeks to 10 years, but most studies lasted 24 weeks or less. Participants were mainly middle-aged, overweight or obese adults of European ancestry who had had diabetes for more than 2 years and no major comorbid conditions. Mean baseline hemoglobin A_{1c} levels ranged from 6% to 12% but were typically between 7% and 9%. About two thirds of studies received pharmaceutical industry support. Only 22 (16%) trials described their randomization techniques, and 83 (61%) reported double-blinding. In 33 (24%) studies, losses to follow-up and reasons for withdrawals were not described.

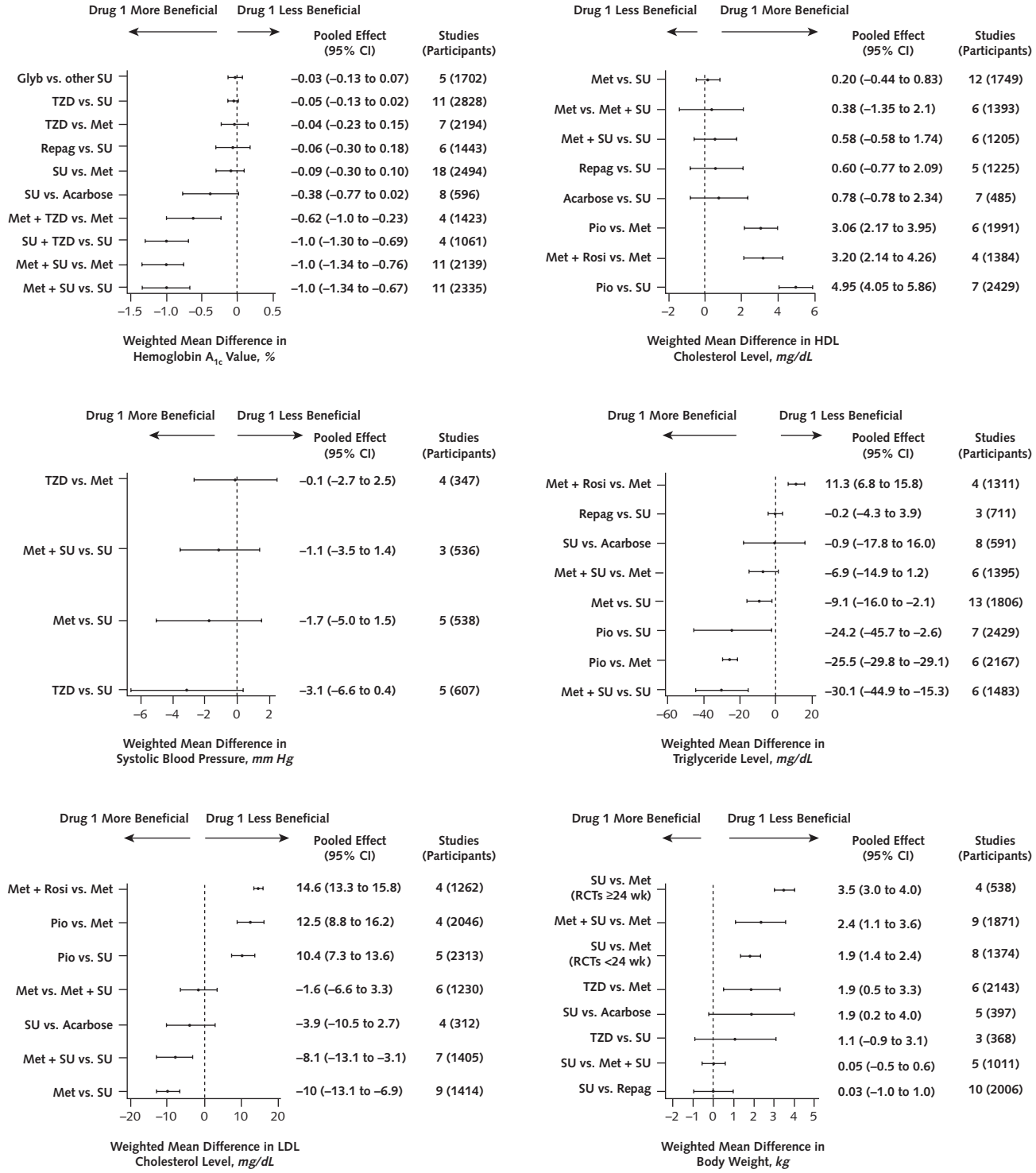
Hemoglobin A_{1c} Level. **Figure 2** shows the comparative effects of oral diabetes agents on hemoglobin A_{1c}. Thiazolidinediones, second-generation sulfonylureas, and metformin produced similar reductions in hemoglobin A_{1c} levels when used as monotherapy (absolute reduction, about 1 percentage point). Repaglinide produced similar reductions in hemoglobin A_{1c} levels compared with sulfonylureas. Combination therapies had additive effects, producing an absolute reduction in hemoglobin A_{1c} levels of about 1 percentage point more than monotherapy.

The results of these meta-analyses were generally consistent with results of the UKPDS, a multicenter randomized trial starting in 1977 that had minimal loss to follow-up (3). After 3 months of dietary intervention, participants were stratified by ideal body weight and randomly assigned to receive insulin, chlorpropamide, glibenclamide, or dietary intervention alone. Overweight participants were also randomly allocated to metformin. All agents had similar effects on hemoglobin A_{1c} levels. After 10 years, glibenclamide and metformin had a statistically insignificant between-group absolute difference of 0.3 percentage point (3, 30–32).

Few head-to-head comparisons involved repaglinide, nateglinide, or α-glucosidase inhibitors. To evaluate these agents, we therefore relied on indirect comparisons with placebo controls. Repaglinide produced similar reductions in hemoglobin A_{1c} levels (about 1 absolute percentage point) when compared indirectly with thiazolidinediones and metformin. In contrast, nateglinide and α-glucosidase inhibitors produced weaker reductions in hemoglobin A_{1c} levels (about 0.5 absolute percentage point). **Appendix Table 1** (available at www.annals.org) shows findings for placebo-controlled trials and the full report on indirect comparisons (20).

Blood Pressure. **Figure 2** shows the comparative effects of oral diabetes agents on blood pressure. Thiazolidinediones, second-generation sulfonylureas, and metformin had similarly minimal effects on systolic blood pressure (mean decrease <5 mm Hg). The greatest contrast was between thiazolidinediones and sulfonylureas—the former agent produced a 3–mm Hg greater reduction—but this difference was not statistically significant. Too few comparisons of meglitinides and acarbose with other oral diabetes agents in terms of blood pressure were available to draw firm conclusions. Results were similar for diastolic blood pressure (data not shown) (20).

Figure 2. **Weighted mean difference in blood pressure, laboratory values, and body weight with use of oral medications for type 2 diabetes mellitus.**



Error bars represent 95% CIs. To convert cholesterol and triglyceride values to mmol/L, multiply by 0.0259 and 0.0113, respectively. Glyb = glyburide; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Met = metformin; Pio = pioglitazone; RCT = randomized, controlled trial; Repag = repaglinide; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione.

Plasma Lipid Levels. **Figure 2** shows the comparative effects of oral diabetes agents on plasma lipid levels. Metformin decreased LDL cholesterol levels by about 0.26 mmol/L (10 mg/dL), whereas thiazolidinediones consistently increased LDL cholesterol levels by a relative mean of 0.26 mmol/L (10 mg/dL). Sulfonylureas had similar minimal effects on LDL cholesterol compared with acarbose or repaglinide (33, 34).

Thiazolidinediones increased HDL cholesterol levels by a mean of 0.08 to 0.13 mmol/L (3 to 5 mg/dL) compared with metformin or second-generation sulfonylureas; these latter agents had little effect on HDL cholesterol. Combination therapy with thiazolidinediones increased HDL cholesterol levels similarly to monotherapy with thiazolidinediones. Repaglinide and acarbose had little effect on HDL cholesterol compared with second-generation sulfonylureas.

Only rosiglitazone increased triglyceride levels, by a mean of 0.11 mmol/L (10 mg/dL) in placebo-controlled trials (data not shown). Pioglitazone decreased triglyceride levels more than metformin, by a mean of 0.29 mmol/L (26 mg/dL), and metformin decreased triglyceride levels more than second-generation sulfonylureas, by a mean of 0.11 mmol/L (10 mg/dL). Repaglinide and acarbose produced similar reductions in triglyceride levels, by a mean of 0.11 to 0.34 mmol/L (10 to 30 mg/dL) compared with second-generation sulfonylureas.

Data on nateglinide were too sparse to draw conclusions about its comparative effects on lipid levels.

Body Weight. Compared with sulfonylureas, thiazolidinediones and repaglinide produced similar gains in body weight (1 to 5 kg). Metformin produced no weight gain compared with most other oral agents or placebo (**Figure 2** and **Appendix Table 2**), and acarbose produced no weight gain compared with placebo (**Appendix Table 2**).

Three UKPDS articles reported weight changes that were consistent with these results favoring metformin over sulfonylurea (mean relative decrease, 2 kg at 10 years of follow-up) (3, 30, 32). Most of the weight gain in the glibenclamide group occurred in the first 2 years, whereas the metformin group maintained body weight in the first 2 years and then experienced weight gain (3).

Comparative Risk for Adverse Events with Oral Diabetes Agents

Summary of Evidence

Several randomized, controlled trials and some observational studies consistently demonstrate that minor and major hypoglycemic episodes are more frequent in adults receiving second-generation sulfonylureas (especially glyburide) than in those receiving metformin or thiazolidinediones. Repaglinide and second-generation sulfonylureas conferred similar risks for hypoglycemia.

In many trials and a few observational studies, metformin was almost always associated with more gastrointestinal problems (flatus, nausea, vomiting, and abdominal pain) than were most other oral diabetes agents. However, rates of lactic acidosis were similar between metformin and other oral diabetes agents, according to a systematic review of 176 comparative trials (35).

In many randomized trials, thiazolidinediones were associated with higher risk for edema than were sulfonylureas or metformin (absolute risk difference, 2% to 21%). Other than edema and hypoglycemia, we had difficulty assessing harms associated with thiazolidinediones because there were few trials and events. In addition, cohort studies often did not adjust for key confounders. Thiazolidinediones appeared to confer a higher risk for congestive heart failure (although absolute risks were small—generally 1% to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared with sulfonylureas and metformin.

Few studies compared the effect of meglitinides with that of other oral diabetes agents for outcomes other than hypoglycemia. Most studies on adverse effects were applicable to persons without major cardiovascular, renal, or hepatic comorbid conditions.

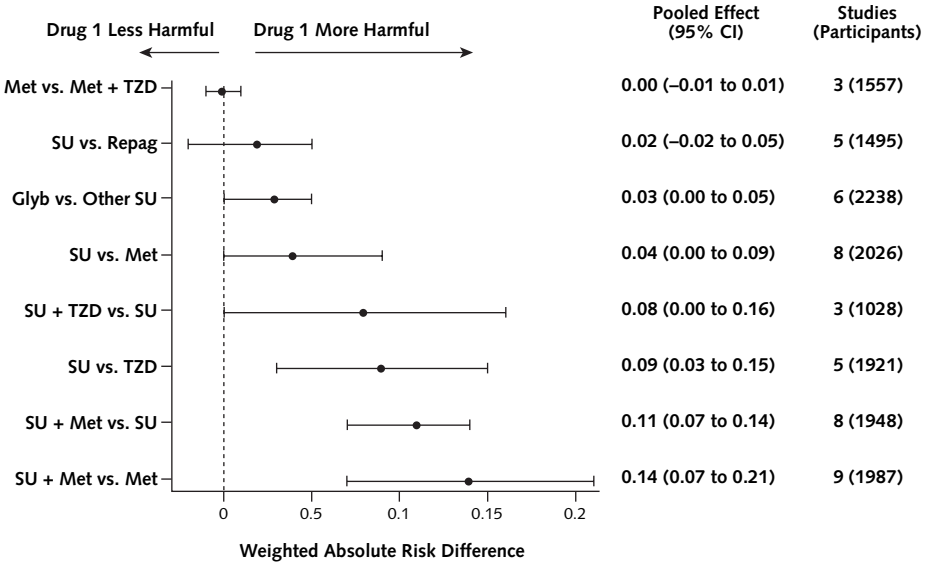
Characteristics and Quality of Studies on Adverse Events

Overall, 167 original articles and 2 Cochrane systematic reviews evaluated adverse events (the full report provides a list of references and detailed evidence tables) (20). About two thirds of the studies were randomized, controlled trials, and the rest were observational. Most were based in the United States or Europe and had industry support. Study duration varied from 3 months to more than 10 years. Most participants were middle-aged to older adults of European ancestry who were overweight or obese. The duration of diabetes ranged from 1 year to 15 years, and mean baseline hemoglobin A_{1c} levels were typically between 7% and 9%. Most randomized, controlled trials excluded people with major cardiovascular, hepatic, or renal disease.

Eighty-five percent (105 of 123) of the randomized, controlled trials with data relevant to adverse events did not describe the randomization technique in sufficient detail to determine whether the randomization was appropriate. About two thirds (66%) of these trials were reported as double-blind. However, 90 (73%) of these trials did not describe the masking procedure. Twenty-two (18%) trials did not report on withdrawals or losses to follow-up.

Hypoglycemia. Minor and major hypoglycemic episodes were more frequent in patients receiving second-generation sulfonylureas (especially glyburide) than in those receiving metformin or thiazolidinediones. Absolute risk differences between groups ranged from 4% to 9% when sulfonylureas were compared with metformin or thiazolidinediones in short-term randomized trials, al-

Figure 3. **Pooled hypoglycemia results for randomized trials, by drug comparison.**



Error bars represent 95% CIs. Glyb = glyburide; Met = metformin; Repag = repaglinide; SU = sulfonylurea; TZD = thiazolidinedione.

though reported levels of hypoglycemic risk ranged widely across studies: 0% to 36% for second-generation sulfonylureas, 0% to 21% for metformin, and 0% to 24% for thiazolidinediones.

The 10-year follow-up from UKPDS reported the annual rates of minor and major hypoglycemia as 17.5% and 2.5%, respectively, in the glibenclamide group (obese and nonobese persons) and 4.2% and 0%, respectively, in the metformin group (obese persons only). Results from observational studies were consistent with those of the UKPDS.

Glyburide and glibenclamide conferred a slightly higher risk for hypoglycemia compared with other second-generation sulfonylureas (absolute risk difference, about 2% in trials of short duration). Repaglinide and second-generation sulfonylureas conferred similar risks for hypoglycemia. Comparative data on acarbose and nateglinide were sparse. The incidence of minor and major hypoglycemia was higher with combinations that included sulfonylureas compared with metformin or sulfonylurea monotherapy (absolute risk differences of 8% to 14% for short-duration trials) (**Figure 3**).

Gastrointestinal Problems. Metformin produced more gastrointestinal symptoms (range, 2% to 63%) than most other oral diabetes agents (range, 0% to 36% for thiazolidinediones, 0% to 32% for second-generation sulfonylureas, and 8% to 11% for repaglinide). The absolute risk differences among groups ranged from 0% to 31%, although most were between 5% and 15%. Acarbose produced percentages of gastrointestinal symptoms (range, 15% to 30%) similar to those with metformin and higher than those with thiazolidinediones and sulfonylureas in a few trials (<3 trials for each comparison). Too few comparative studies were available on nateglinide to draw firm conclusions (**Table 2**).

Elevated Aminotransferase Levels and Liver Failure. Currently marketed thiazolidinediones, second-generation sulfonylureas, and metformin had similarly low rates (generally <1%) of clinically significant elevated aminotransferase levels (>1.5 to 2 times the upper limit of normal). An insufficient number of studies evaluated or reported on the effects of meglitinides on serum aminotransferase levels, but they appeared to be similar to the effects of other oral diabetes agents (**Table 2**). Liver failure was so rare that agents could not be compared for this outcome by using these data.

Congestive Heart Failure. Risk for congestive heart failure was greater with thiazolidinediones as monotherapy or combination therapy than with metformin or sulfonylureas (range of absolute risk differences, 0.7% to 2.2% in head-to-head, short-duration randomized trials). The absolute risk for congestive heart failure in the trials ranged from 0.8% to 3.6% for thiazolidinediones and 0% to 2.6% for nonthiazolidinediones. In contrast, neither metformin nor second-generation sulfonylureas were associated with congestive heart failure risk in 2 of 3 observational studies and 2 of 2 placebo-controlled trials. Congestive heart failure was reported mostly in cohort studies that did not adjust for key confounders, such as duration of diabetes, hemoglobin A_{1c} level, blood pressure, and medication adherence. However, the cohort studies were consistent with one another and with limited data from randomized trials (**Table 2**).

Peripheral Edema. Edema was more frequent in patients receiving thiazolidinediones as monotherapy or com-

bination therapy (range, 0% to 26%) than in patients receiving second-generation sulfonylureas (range, 0% to 8%) or metformin (range, 0% to 4%). The absolute risk differences ranged from 2% to 21% in head-to-head randomized trials (**Table 2**).

Lactic Acidosis. We found a systematic review that reported similar rates of lactic acidosis between metformin and other oral diabetes agents (35). In this review, pooled data from 176 comparative trials and cohort studies totaling 35 619 patient-years revealed no cases of fatal or nonfatal lactic acidosis in any medication group. The estimated hypothetical upper limit of the underlying incidence of lactic acidosis was 8.4 cases per 100 000 patient-years in the metformin group and 9 cases per 100 000 patient-years in the nonmetformin group (35). We found 8 additional studies with data on lactic acidosis (3 randomized trials and 5 cohort studies). All showed little or no elevated risk for lactic acidosis in metformin recipients (**Table 2**).

Anemia, Leukopenia, and Thrombocytopenia. Six head-to-head randomized trials, 7 placebo-controlled random-

Table 2. **Adverse Effects Related to Oral Diabetes Medications in Head-to-Head Comparisons***

Comparison	Study Type	Studies, *n*†	Participants, *n*‡	Range in Risk Estimates§
Congestive heart failure				
TZD vs. sulfonylurea	RCTs	2	376	1.0% to 2.2%
Sulfonylurea + TZD vs. sulfonylurea	RCTs	3	1028	0.7% to 1.2%
TZD vs. non-TZD	Cohort	3	73 914	1.06 to 2.27‖
	Case–control	1	1940	1.37‖
Edema				
TZD vs. metformin	RCTs	4	2712	2.4% to 10.5%
	Cohort	1	72	0.35%
TZD vs. sulfonylurea	RCTs	5	1921	4.2% to 21.2%
	Non-RCT	1	36	16.7%
	Cohort	1	132	6.6%
TZD vs. meglitinides	RCTs	2	248	2% to 3%
Metformin + TZD vs. metformin	RCTs	3	1439	2% to 5.2%
Sulfonylurea + TZD vs. sulfonylurea	RCTs	3	1028	6.6% to 14%
Gastrointestinal problems				
Metformin vs. TZD	RCTs	3	2038	7.9% to 13%
	Cohort	1	71	−26% (metformin vs. pioglitazone) to 10.4% (metformin vs. rosiglitazone)¶
Metformin vs. sulfonylurea	RCTs	10	2313	0.4% to 31%
	Cross-sectional	2	524	5% to 14%
	Cohort	1	209	7.9%
Sulfonylurea vs. TZD**	RCTs	3	1679	0.5% to 1.0%
Metformin vs. meglitinides	RCTs	2	469	2.8% to 3.6%
Metformin vs. metformin + sulfonylurea	RCTs	10	2137	−4.3% to 28%
	Cross-sectional	1	99	0%
Metformin + sulfonylurea vs. sulfonylurea	RCTs	11	2794	−4.8% to 20%
	Cross-sectional	1	99	14%
Aminotransferase levels ≥1.5 times the upper limit of normal				
TZD vs. metformin	RCTs	2	1271	0.0% to 0.1%
	Cohort	1	2274	−0.2%
Sulfonylurea vs. TZD	RCTs	3	1548	0% to 1.1%
	Non-RCT	1	36	0%
	Cohort	1	2274	0.4%
Meglitinides vs. TZD	RCTs	2	248	0% to 1.6%
TZD vs. non-TZD	RCTs	2	137	0%
Metformin vs. metformin + TZD	RCTs	2	791	0.7% to 1.8%
Sulfonylurea vs. sulfonylurea + TZD	RCTs	2	693	0% to 0.4%
Lactic acidosis				
Metformin vs. nonmetformin	Systematic review	1	35 619††	0%
	RCTs	3	9227	0% to 3%

* Head-to-head comparisons for which more than 1 study was available are included. RCT = randomized, controlled trial; TZD = thiazolidinedione.
† Studies with available data on risk estimates (differences in percentage of adverse events).
‡ Reported as the number of study participants, unless otherwise indicated.
§ Reported as the percentage of risk difference, unless otherwise indicated.
‖ Odds ratio.
¶ One study showed both pioglitazone versus metformin and rosiglitazone versus metformin, which had different results.
** In 2 of these trials, metformin was added to both the TZD and sulfonylurea groups.
†† Patient-years. There were 8.4 cases per 100 000 patient-years.

ized trials, and 1 cohort study evaluated anemia as an outcome. Thiazolidinediones may be associated with an increased risk for anemia compared with other oral diabetes agents (posttreatment absolute risk differences, 1% to 5%). The mean decrease in hemoglobin level was small (≤1 g/dL). Only 1 study reported an adverse event of thrombocytopenia and leukopenia.

Serious Allergic Reactions. No study reported an allergic reaction to oral diabetes medications that led to hospitalization or death.

Unpublished Data on Harms

In addition to data published in peer-reviewed journals, we reviewed data from the FDA, unpublished trials conducted by industry, and clinical trial registries. The only new finding was that pioglitazone was associated with an increased risk for hospitalization for acute cholecystitis (12 patients) compared with placebo (1 patient) in a pooled analysis of 1526 patients (20). Otherwise, unpublished data were consistent with those from the published literature.

Publication Bias

We did not find strong evidence of possible publication bias. Only 2 drug comparisons, from studies of hypoglycemia, had statistically significant results for publication bias ($P < 0.05$) according to the less conservative test of Egger and colleagues (27): metformin versus second-generation sulfonylureas (8 studies; $P = 0.04$) and repaglinide versus placebo (3 studies; $P = 0.035$). The 3 largest studies in the comparison of metformin with sulfonylureas had smaller absolute risk differences than the smaller studies; however, all studies showed that metformin is associated with less hypoglycemia than sulfonylureas. There were too few studies in the comparison of repaglinide versus placebo to draw conclusions about publication bias. For all other comparisons, the funnel plots appeared to be roughly symmetrical, and results of the tests of Begg and Mazumdar (26) and Egger and colleagues (27) were not statistically significant.

DISCUSSION

Ideally, oral diabetes agents should improve microvascular and macrovascular outcomes and mortality. We found no definitive comparative evidence on these outcomes. Because of this uncertainty, we evaluated medication effects on intermediate outcomes and other adverse events. By these criteria, we found that metformin was similar to, or better than, other currently available oral agents. Second-generation sulfonylureas also fared well against other agents, apart from the increased risk for hypoglycemia. Compared with newer agents, metformin and second-generation sulfonylureas share 3 additional advantages: lower cost, longer use in practice, and more intensive scrutiny in long-term trials with clinically relevant end points. Thiazolidinediones, although they pose a lower risk for hypoglycemia and a slight beneficial effect on HDL cholesterol level, showed no advantage in glucose-lowering effect and were associated with adverse effects on LDL cholesterol level, body weight, and risk for congestive heart failure.

These findings support the current American Diabetes Association and International Diabetes Federation recommendations that favor metformin as initial pharmacotherapy for type 2 diabetes (36, 37). They are also consistent with the 2007 American College of Endocrinology guidelines that suggest choosing an oral diabetes agent on the basis of the individual patient's burden of comorbid conditions (38). Of course, optimal glycemic control often requires multidrug therapy. Our review confirms that a second agent is additive both in terms of improved glycemic control and increased risk for adverse events, unless both agents are used at lower doses. Although they are not clearly superior to newer agents, sulfonylureas remain a reasonable alternative as second-line therapy, especially if cost is an issue.

Our findings are generally consistent with those of previous reviews of the effects of oral diabetes agents on intermediate outcomes, such as hemoglobin A_{1c} level, lipid levels, and body weight (10, 12, 14, 16, 18, 19, 39, 40). Inzucchi (18) conducted a systematic review of the effect of oral diabetes agents and placebo on hemoglobin A_{1c} and drew conclusions similar to ours. Our study adds to this research by including more recent articles, comparisons involving meglitinides, and meta-analyses of head-to-head comparisons. In a 2002 systematic review (without quantitative meta-analyses) on the lipid effects of oral diabetes medications, Buse and coworkers (19) reported findings similar to ours. Our investigation updates their review and adds more detail on differences between drugs from formal meta-analyses. The main contribution of our review is its comprehensiveness: We included a broad range of clinically relevant outcomes and adverse effects across all available drug classes.

Nissen and Wolski (11) recently reported results of a meta-analysis suggesting a relationship between use of rosiglitazone and risk for myocardial infarction. When they analyzed specific drug–drug or drug–placebo comparisons, however, their results were not statistically significant. Likewise, we found no statistically significant differences between specific oral diabetes medications in terms of cardiovascular outcomes other than congestive heart failure. Limitations of Nissen and Wolski's study included the small number of largely unadjudicated events and the fact that cardiovascular events were not the primary outcome. An additional limitation that influenced their conclusions was the decision to include studies with 2 diverse patient samples: nondiabetic persons, in whom the risk-to-benefit ratio of an oral diabetes agent may differ greatly from that in their diabetic counterparts, and diabetic persons with congestive heart failure, for whom rosiglitazone is contra-

indicated. The decision to include these studies may have biased the meta-analysis toward showing harm. Finally, exclusion of studies with no cardiovascular events in either group introduced a small bias against finding no difference in cardiovascular risk. Given the limitations of Nissen and Wolski's analysis, the effects of rosiglitazone on cardiovascular mortality and myocardial infarction are still uncertain. A recently published interim analysis from the RECORD study showed no statistically significant elevation in cardiovascular risk (besides congestive heart failure) related to rosiglitazone compared with metformin and sulfonylureas (20). Overall, these recent findings are consistent with ours: We found no conclusive evidence of worse cardiovascular morbidity or mortality with oral diabetes agents, other than the higher risk for congestive heart failure with thiazolidinediones than with other oral medications.

Several adverse events merit further discussion. First, because of concerns about lactic acidosis, metformin is contraindicated in patients with impaired renal function or congestive heart failure. However, neither our review nor that of Salpeter and colleagues (35) found evidence of an elevated risk for lactic acidosis in patients taking metformin compared with other oral diabetes agents. The evidence for metformin-induced lactic acidosis stems mainly from about 300 case reports. We did not consider case reports in our review because they pose problems in determining causality and provide no clear denominator for risk estimation. Underlying comorbid conditions, such as chronic kidney disease or myocardial infarction, are well-established risk factors for lactic acidosis; therefore, attributing lactic acidosis to metformin use versus an underlying comorbid condition is often difficult. Most reported cases of metformin-related lactic acidosis were associated with severe underlying illnesses (41, 42). Because of lingering fears about biguanides (phenformin was unequivocally related to risk for lactic acidosis), we suspect that apparent cases of "metformin-induced lactic acidosis" may have been overreported. However, we could not rule out the possibility that metformin conferred additional risk in the presence of severe underlying cardiac or renal disease, because these conditions were excluded in most randomized trials and were too uncommon in cohort studies to allow assessment.

Second, macular edema has been mentioned as an adverse event related to use of rosiglitazone only in case reports (43), which we excluded from our review. Third, the ADOPT study (published after our review was completed) reported an increase in fracture risk in women taking rosiglitazone compared with metformin or sulfonylureas (28). No cases were reported in the studies from our review, but this will need further investigation. Finally, repaglinide may be associated with less serious hypoglycemia compared with second-generation sulfonylureas, as was seen in 1 study of elderly persons (44), and in patients who skip meals, as was seen in 1 randomized trial not included in our review (because it was <3 months in duration) (45).

Our study has limitations. First, most of the trials, especially those of newer agents, were short-term trials, generally lasting less than 1 year. Ideally, therapeutic decision making should be based on long-term effectiveness. Second, head-to-head data were limited in many instances. This was especially true for multidrug regimens now in common use and for some of the newer agents, such as rosiglitazone, nateglinide, and miglitol. Third, although almost all studies reported the incidence of hypoglycemia, reporting of other adverse events was inconsistent, and the definitions of adverse events varied across studies. For instance, gastrointestinal events could include nausea, vomiting, abdominal pain, flatulence, or a combination of these events, making comparisons across studies difficult. Few trials reported data on elevated liver aminotransferase levels, congestive heart failure, anemia, and allergic reactions; therefore, we relied on cohort studies for many of these outcomes. The available cohort studies, however, were limited by their ability to adjust for key confounding factors, such as hemoglobin A_{1c} level, blood pressure, duration of diabetes, adherence to medications, and medication dose. Finally, we focused on safety issues by making an a priori hypothesis of potential harm, and we may have missed harms reported only in case reports or those that were not assessed in trials or observational studies.

Compared with newer, more expensive agents (thiazolidinediones, α-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control and other cardiovascular risk factors (blood pressure, lipid levels, and body weight). Each oral diabetes agent is associated with adverse events that counterbalance its benefits. Overall, metformin seemed to have the best profile of benefit to risk. Large, long-term comparative studies on major clinical end points, such as myocardial infarction, chronic kidney disease, and cardiovascular mortality, are needed to determine definitively the comparative effects of the oral diabetes agents, especially in light of recent controversy regarding rosiglitazone.

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Appendix Table 1. **Summary Measures: Weighted Mean Absolute Difference in Hemoglobin A_{1c} Level between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet**

Comparison*	Studies with Data on Mean Differences, *n*	Weighted Mean Absolute Difference in Hemoglobin A_{1c} Level between Groups (95% CI), %
Pioglitazone vs. control	9	−0.97 (−1.18 to −0.75)
Rosiglitazone vs. control	8	−1.16 (−1.39 to −0.92)
Metformin vs. control	15	−1.14 (−1.4 to −0.87)
Sulfonylureas vs. control	11	−1.52 (−1.75 to −1.28)
Repaglinide vs. control	4	−1.32 (−1.9 to −0.8)
Nateglinide vs. control	4	−0.54 (−0.8 to −0.27)
Acarbose vs. control	28	−0.77 (−0.9 to −0.64)

* The control group consisted of placebo or diet.

Appendix Table 2. **Summary Measures: Weighted Mean Absolute Difference in Body Weight between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet**

Comparison*	Studies with Data on Mean Differences, *n*	Weighted Mean Absolute Difference in Body Weight between Groups (95% CI), *kg*
Pioglitazone vs. control	6	3.0 (2.0 to 3.9)
Rosiglitazone vs. control	4	3.1 (1.1 to 5.1)
Metformin vs. control	8	0.3 (−0.3 to 0.9)
Sulfonylureas vs. control	4	3.8 (3.6 to 4.0)
Meglitinides vs. control	2	Not applicable
Acarbose vs. control	16	−0.1 (−0.5 to 0.2)

* The control group consisted of placebo or diet.