Effective Health Care

Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes

Executive Summary

Background

Type 2 diabetes is characterized by insulin resistance accompanied by progressive deficiency in insulin secretion. Type 2 diabetes is an increasingly common disease that is closely associated with obesity. In 2005, the prevalence of Americans with diagnosed type 2 diabetes was 2.4 percent for adults aged 20-39 years, 10 percent for adults aged 40-59 years, and 21 percent for adults aged 60 years or over. From 1980 through 2004, the number of Americans diagnosed with diabetes more than doubled, from 5.8 million to 14.7 million. Observational studies and clinical trials show that improved glycemic control reduces microvascular complications (e.g., complications involving the eyes, kidneys, or nerves) and may reduce macrovascular complications (e.g., heart attack); however, the effects of specific oral diabetes medications on these outcomes are less certain.

As new classes of medications have become available for the treatment of diabetes, clinicians and patients have faced a bewildering array of oral medications with different mechanisms of action. The first oral diabetes medications were sulfonylureas, which were introduced into the market in 1955. The second-generation sulfonylureas, which are used today, were

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introduced in 1984. Metformin (a biguanide) was introduced in 1995, meglitinides in 1997, alpha-glucosidase inhibitors in 1998, and thiazolidinediones in 1999. Although most experts consider the alpha-glucosidase inhibitors to be inferior to the other drug classes in terms of efficacy, clinicians may find it difficult to choose between the other four drug classes that are now in common use. Generally, clinicians must choose between older, less expensive medications such as a second-generation sulfonylurea or metformin and the newer, more expensive medications such as a thiazolidinedione or meglitinide. In addition, clinicians must consider concerns about specific medications conferring excess cardiovascular risks when compared with other oral diabetes medications or placebo.

The well-known United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that oral diabetes medications may have similar effects on cardiovascular morbidity and mortality when they have similar effects on glycemic control. However, the UKPDS was conducted prior to the emergence of thiazolidinediones and statins.

Several systematic reviews of oral diabetes medications shed light on differences in short-term and long-term outcomes. However, only two reviews have compared all of the oral diabetes medications used commonly in the United States.

In 2002, Inzucchi and colleagues from Yale University found that: (1) most diabetes medications lower hemoglobin A1c (HbA1c) by an absolute reduction of 1-2 percent,[1] with equivalent efficacy across medications, except for alpha-glucosidase inhibitors, which decrease HbA1c by 0.5-1 percent; (2) medications in combination confer additional glycemic benefits; (3) long-term micro- or macrovascular risk reduction was demonstrated only with sulfonylureas and metformin.

In 2004, Buse and colleagues from the University of North Carolina compared effects on serum lipid levels among all the oral diabetes medications. They found that only metformin, acarbose, voglibose, rosiglitazone,

and pioglitazone had significant effects on the lipid profile. Metformin at high doses and pioglitazone both reduced triglycerides, while acarbose, rosiglitazone, and pioglitazone increased high-density lipoproteins. Lastly, acarbose decreased low-density lipoproteins, while rosiglitazone increased low-density lipoproteins.

Many outcomes besides HbA1c and lipid levels are important when evaluating and comparing oral diabetes medications, such as blood pressure control, weight changes, microvascular and macrovascular disease, adverse events, and mortality. It is critical to evaluate adverse events, since these affect adherence as well as morbidity and mortality. Additionally, certain diabetes medications may be less safe for patients with comorbid conditions. For instance, biguanides such as metformin are contraindicated in patients with renal or liver failure because of a potentially higher risk of lactic acidosis. To date, no study has evaluated proximal clinical measures, long-term effects, and adverse events among oral diabetes medications used in the United States. If they could compare the short- and long-term effects as well as the adverse effects of these medications, clinicians might have a better sense of when to use which oral diabetes medication. This review will be helpful as new classes of oral diabetes medications, such as the dipeptidyl peptidase IV (DPP-IV) inhibitors, emerge on the market. Furthermore, it may help policymakers and insurers to have better insight when deciding on policies relating to medication coverage.

This report summarizes the available evidence comparing the efficacy and safety of oral diabetes medications in the treatment of type 2 diabetes. The report addresses the following key questions:

1. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical outcomes: glycated hemoglobin, weight, blood pressure, serum lipid levels, and 2-hour postprandial glucose (PPG) levels?

2. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect distal diabetes-related complications including mortality and the following macrovascular and microvascular complications: coronary artery disease, myocardial infarction, stroke, transient ischemic attack, arrhythmia, coronary artery stenosis and in-stent restenosis,

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[1] One characteristic of type 2 diabetes is an elevation of the proportion of HbA1c in the blood from a normal level of 6.5 to 7 percent to an elevated level of >6.5 to 7 percent (e.g., 10 percent). In this report, an "absolute" reduction of 1 percent means a reduction of one percentage point in that proportion (e.g., from 10 percent to 9 percent).

retinopathy, nephropathy, neuropathy, and peripheral arterial disease?

3. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to influence other health outcomes, including quality of life and functional status?

4. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in terms of risk of the following life-threatening adverse events: life-threatening hypoglycemia leading to emergency care or death; liver failure; congestive heart failure (CHF); severe lactic acidosis; cancer; anemia, thrombocytopenia, or leucopenia requiring transfusion; and allergic reactions leading to hospitalization or death?

5. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their safety for the following adverse events that are not life threatening: hypoglycemia requiring any assistance; elevated aminotransferase levels; pedal edema; hypervolemia; anemia, thrombocytopenia, and leucopenia not requiring transfusion; mild lactic acidosis; and gastrointestinal (GI) problems?

6. Do safety and effectiveness of oral diabetes medications for the treatment of adults with type 2 diabetes differ across particular adult populations, such as those based on demographic factors (e.g., race/ethnicity, age greater than 65 years, or gender) or comorbid conditions (e.g., renal insufficiency, CHF, liver disease, obesity, depression, or schizophrenia)?

Conclusions

Summary Table A presents the main conclusions from published evidence regarding the comparative effectiveness of oral diabetes medications, organized by key question and type of outcome. The summary table also includes our rating of the level of evidence that supports each conclusion. Meta-regression was conducted using study-level characteristics such as dose of medication, study duration, and study quality. When important differences arose based on these characteristics, we reported them in the table.

In Summary Table B we present a short synopsis of the comparative effectiveness of the oral diabetes medications used most often and for which there were

sufficient data to make comparisons. In each column of the summary table, we indicate the medication that had a better effect on the listed outcome or note when there were at least a moderate number of studies in which no apparent difference was detected.

The text below summarizes the conclusions regarding the main comparisons of interest by outcome, and qualifies points noted in the summary tables.

Comparisons of effects of oral diabetes medications

Glycemic control (hemoglobin A1c). Based on direct data from randomized controlled trials, most oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, metformin, and repaglinide) had similar reductions in hemoglobin A1c (~1-percent absolute reduction) compared with one another as monotherapy. Indirect data, in addition to a few head-to-head trials, showed that nateglinide and alpha-glucosidase inhibitors were less efficacious in reducing hemoglobin A1c as monotherapy (~0.5-percent absolute reduction). Combination therapies had an additive effect and were better at reducing HbA1c compared with monotherapy regimens (~1-percent absolute reduction).

Weight. Weight increased by 1-5 kg with most of the oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and repaglinide), but not for metformin and acarbose, which had no effect on weight in placebo-controlled trials. In direct comparisons with thiazolidinediones and second-generation sulfonylureas, metformin caused relative weight loss. However, this might be an artifact reflecting the withdrawal from a prior sulfonylurea (and withdrawal of its weight-increasing effect) that often occurred in head-to-head trials. There were too few comparative studies of nateglinide to draw conclusions.

Different types of weight gain (central vs. peripheral) may have different effects on morbidity, with central adiposity considered to have greater prediction of cardiovascular outcomes. Only a few studies evaluated whether weight gain was related to increases in visceral adipose tissue, subcutaneous fat, or plasma volume. Therefore, it is unclear whether the weight gains caused by the different medications are physiologically equivalent.

Systolic and diastolic blood pressure. Most oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and metformin) had similarly minimal effects on systolic and diastolic blood pressure (<5 mm Hg). Too few studies compared meglitinides and acarbose with other oral diabetes medications to draw firm conclusions. There was a suggestion of decreased blood pressure in the thiazolidinedione group when compared with second-generation sulfonylureas and acarbose. However, the clinical relevance of these small nonsignificant between-group differences of 3-5 mmHg is questionable.

Low-density lipoprotein. Only thiazolidinediones consistently increased low-density lipoprotein (by about 10 mg/dL), while only metformin consistently decreased low-density lipoprotein (by about 10 mg/dL). Of the two thiazolidinediones, rosiglitazone increased low-density lipoprotein cholesterol more than pioglitazone (difference of about 10-15 mg/dL). In addition, second-generation sulfonylureas showed similar minimal effects on low-density lipoprotein cholesterol when compared with repaglinide and alpha-glucosidase inhibitors. Too few studies on nateglinide were available to draw conclusions.

High-density lipoprotein. Only thiazolidinediones increased high-density lipoprotein. Thiazolidinediones increased high-density lipoprotein by about 3-5 mg/dL, compared with metformin or second-generation sulfonylureas, which had little effect on high-density lipoprotein. Meglitinides had little effect on high-density lipoprotein, but there were too few trials to draw comparative conclusions. Combination therapy with thiazolidinediones increased high-density lipoprotein similarly to monotherapy with thiazolidinediones, while combination therapies without thiazolidinediones had little effect on high-density lipoprotein levels.

Triglyceride levels. Most oral diabetes medications (pioglitazone, metformin, second-generation sulfonylureas, acarbose, and repaglinide) decreased triglycerides, except for rosiglitazone, which generally increased triglycerides. Pioglitazone decreased triglycerides more than metformin (difference of about 26 mg/dL), and metformin decreased triglycerides to a greater degree than second-generation sulfonylureas (difference of about 10 mg/dL). These small differences in triglyceride reduction may reflect differences between groups in initial triglyceride levels that were present despite randomization. Repaglinide and acarbose had similar reductions in triglycerides when compared with second-generation sulfonylureas. There were too few comparisons for nateglinide to draw conclusions.

All-cause mortality. There were too few studies to support any conclusions about how mortality differed between the medications. It was unclear whether effects on mortality differed between the combination of metformin with a sulfonylurea and monotherapy with a sulfonylurea or metformin, due to lack of adjustment for key confounders in cohort studies and lack of studies evaluating this combination. Other comparisons between drugs had too few studies to draw conclusions.

Cardiovascular mortality and morbidity. There were too few studies to support any conclusions about how cardiovascular morbidity or mortality differed between the medications. It was unclear whether cardiovascular mortality differed between the combination of metformin with a sulfonylurea and monotherapy with a sulfonylurea or metformin, due to lack of adjustment for key confounders in cohort studies and lack of studies evaluating this combination. Only pioglitazone and metformin improved cardiovascular morbidity when compared with placebo or diet (one study each, PROactive and UKPDS).

Peripheral vascular disease. Only two randomized controlled trials reported information on peripheral vascular disease, making it difficult to draw conclusions. In the largest of the two trials (PROactive), pioglitazone had no effect on peripheral vascular disease when compared with placebo in subjects with a history of cardiovascular disease.

Microvascular outcomes. Few studies examined how microvascular outcomes differed between the medications, but some differences were reported. In the UKPDS, glibenclamide decreased the need for photocoagulation and had a protective effect on combined microvascular outcomes (retinopathy plus nephropathy) compared with the conventional arm (diet), while metformin showed no effect on retinopathy compared with the conventional arm. Pioglitazone may be better at reducing short-term nephropathy compared with metformin, based on two short-duration randomized controlled trials.

Quality of life and functional status. No conclusions could be drawn regarding the comparative effects of the medications on quality of life and functional status

because of a limited number of studies and differences in the questionnaires used to assess quality of life.

Hypoglycemia. Minor and major hypoglycemic episodes were more frequent in subjects taking second-generation sulfonylureas (especially glyburide) than in subjects taking other oral diabetes medications except repaglinide. Reported percentages of subjects experiencing minor or major hypoglycemic episodes ranged from 0 to 58 percent for second-generation sulfonylureas vs. 0 to 21 percent for metformin and 0 to 24 percent for thiazolidinediones. The absolute risk difference was 5-10 percent when comparing second-generation sulfonylureas with metformin or thiazolidinediones. Glyburide/glibenclamide had a higher risk of hypoglycemia compared with other second-generation sulfonylureas (absolute risk difference of ~2 percent). Repaglinide and second-generation sulfonylureas had a similar incidence of subjects with hypoglycemia. However, repaglinide may be associated with less serious hypoglycemia in the elderly and in people who skip meals. Data were sparse on the comparisons between acarbose or nateglinide and other oral diabetes medications. The incidence of minor and major hypoglycemia was higher with combinations that included sulfonylureas, compared with metformin or sulfonylurea monotherapy (absolute risk differences of 8-14 percent). The combination of metformin plus rosiglitazone had a similar risk of minor hypoglycemia compared with metformin monotherapy, and no serious events occurred in either of these treatment groups.

Gastrointestinal adverse events/problems. Metformin and acarbose were generally associated with a higher percent of subjects with GI adverse events (range 2-63 percent and 15-30 percent, respectively) compared with other oral diabetes medications (thiazolidinediones: range 0-36 percent, second-generation sulfonylureas: range 0-32 percent, and meglitinides: range 8-11 percent). The absolute risk differences ranged from 5 to 15 percent when comparing metformin or acarbose with these other oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, or meglitinides). Metformin monotherapy was associated with more frequent adverse events compared with the combination of metformin plus a second-generation sulfonylurea or metformin plus a thiazolidinedione if the metformin component was at a lower dose than the metformin monotherapy arm.

Elevated aminotransferase levels/liver failure. Several oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and metformin) had similarly low rates (less than 1 percent) of clinically relevant elevated aminotransferase levels (greater than 1.5 to 2 times the upper limit of normal). Insufficient studies evaluated or reported on the effects of meglitinides on serum aminotransferase levels, but their effects appeared to be similar to the effects of other oral diabetes medications. The evidence was insufficient to compare oral diabetes medications on the outcome of liver failure since there were too few events.

Congestive heart failure. Thiazolidinediones were associated with greater risk of CHF compared with metformin or sulfonylureas (two head-to-head randomized controlled trials with absolute risk differences of 1-2 percent; cohort studies had a range in odds ratios of 1.06-2.27, which was significant in four of five head-to-head studies). Metformin and second-generation sulfonylureas had similarly little impact on the incidence of CHF. CHF was reported mostly in cohort studies that did not adjust for key confounders, such as duration of diabetes, HbA1c level, blood pressure level, and medication adherence. However, the cohort studies were consistent with one another and were consistent with the data found in the randomized controlled trials, making these conclusions likely to be accurate.

Edema. Edema was more frequent in subjects taking thiazolidinediones (range 0-26 percent) than in subjects taking second-generation sulfonylureas (range 0-8 percent) or metformin (range 0-4 percent). The absolute risk differences ranged from 2 to 21 percent when comparing thiazolidinediones with second-generation sulfonylureas or metformin. No cases of macular edema were identified in the studies reviewed; however, case reports were excluded from the review, and this is where most macular edema cases have been identified. Cohort studies are needed to explore the issue of macular edema further. Data were too sparse to draw conclusions about how the incidence of edema may differ between other oral diabetes medications.

Lactic acidosis. Despite traditional concerns, the rate of lactic acidosis was similar between metformin and other oral diabetes medications or placebo (8.4 vs. 9 cases per 100,000 patient-years). We did not have enough information on subjects taking metformin with chronic conditions such as chronic renal insufficiency,

chronic liver disease, congestive heart failure, or severe pulmonary disease; therefore, we were unable to determine the safety of taking metformin in the presence of comorbid conditions that predispose subjects to lactic acidosis.

Anemia, thrombocytopenia, and leucopenia. Thiazolidinediones may be associated with an increased risk of anemia (range 0-7 percent) compared with other oral diabetes medications (range 0-3 percent). The absolute risk differences ranged from ~1-5 percent when comparing thiazolidinediones with other oral diabetes medications. The decrease in hematocrit was small (1 g/dL) and would not be clinically relevant except for subjects with severe or borderline severe anemia. Only one study reported an adverse event of thrombocytopenia and leucopenia, making comparisons between medications impossible.

Differences in effectiveness between subgroups of patients with type 2 diabetes

Data were insufficient to support any conclusions regarding differences in effectiveness of the medications between subgroups of patients with type 2 diabetes.

Remaining Issues

The review of existing evidence identified a number of issues requiring further research. These specific research issues are grouped by key question below.

For Key Question 1 (proximal clinical outcomes)

▶ Future studies should examine effects of medications on glycemic variability using standardized methods to better compare effects across medications. Studies should consistently report 2-hour postprandial glucose as well as measure effects over time pre- and post-treatment.

▶ There were few extended studies to characterize the persistence of effects on glycemic control, weight, and lipids over time. Evaluating the durability of effects on proximal outcomes will be helpful in determining the clinical relevance of different effects on lipids, weight, and glycemic control. Linking these effects to cardiovascular outcomes will also help clarify the clinical relevance.

▶ More head-to-head monotherapy trials of rosiglitazone with metformin and sulfonylurea monotherapy are needed to better assess potential differences in lipid effects.

▶ Future studies on weight should attend to effects on body composition and partition effects on weight or body mass index as an increase in fluid, subcutaneous tissue, or visceral adipose tissue, as these may have different effects on health. If possible, investigators should then link these with hard outcomes, such as morbidity and mortality. Furthermore, since sulfonylureas and thiazolidinediones increase weight as monotherapy, future studies need to identify whether there would be an additive or synergistic effect on weight for combinations of sulfonylureas with thiazolidinediones.

For Key Question 2 (distal diabetes-related complications)

▶ More randomized controlled trials and prospective cohort studies should compare the effects of oral diabetes medications on the long-term outcomes of all-cause and cardiovascular mortality, cardiovascular disease morbidity, microvascular disease, and peripheral vascular disease.

▶ Such studies should examine surrogate markers of cardiovascular disease such as carotid intimal media thickness using ultrasound imaging, as well as restenosis rates and arrhythmias.

▶ To determine whether oral diabetes medications differ in their effects on mortality and cardiovascular morbidity, a long-term head-to-head randomized controlled trial should compare thiazolidinediones, metformin, sulfonylurea, and metformin plus a sulfonylurea in subjects with a history of mild macrovascular disease.

▶ To improve understanding of the effects of oral diabetes medications on peripheral vascular disease, studies should use earlier clinically relevant outcomes for peripheral vascular disease, such as ankle brachial index, distance to onset of pain, stopping time during standardized walking, and symptoms, as well as distal outcomes of amputation and death from peripheral vascular disease.

- To improve understanding of the effects of oral diabetes medications on nephropathy, studies should evaluate long-term clinically relevant nephropathy outcomes (such as time to dialysis) as well as short-term proteinuria outcomes.

For Key Question 3 (quality of life)

- More studies should examine the effects of oral diabetes medications on health-related quality of life using standardized, validated questionnaires, especially since quality of life may affect whether patients adhere to medications.

For Key Questions 4 and 5 (adverse effects)

- Studies on oral diabetes medications need to report consistently withdrawals and reasons for withdrawals to improve understanding of potential differences in adverse effects.

- Studies on oral diabetes medications need to report their definitions of adverse events more thoroughly, and consistently report all adverse events (not using aggregated events).

- Additional observational studies of metformin compared with other oral diabetes medications in subjects prone to lactic acidosis would help determine the safety of using this medication in populations with comorbid diseases.

- Further observational studies should evaluate the incidence of (1) macular edema with thiazolidinediones, (2) anemia requiring transfusion or hospital admission for thiazolidinediones compared with other oral agents, and (3) allergic reactions in all oral diabetes medications.

- Further observational studies should evaluate cancer and allergic reactions for all oral diabetes medications.

For Key Question 6 (differences across specific populations)

- To determine differences in medication effectiveness based on comorbidity or demographics, analyses should be stratified or adjusted based on comorbidity or demographics. Specific areas to focus on would be effects of

medications in the elderly and in subjects with and without renal disease, congestive heart failure, liver disease, or psychiatric disease.

Other general issues

- Future observational studies could improve understanding of the effects of oral diabetes medications on adverse events and distal outcomes if they carefully assess key confounders, such as duration of diabetes, adherence to medications, dosing of medications, hemoglobin A1c levels, and blood pressure levels.

- Studies need to report consistently between-group changes from baseline, as well as measures of dispersion such as standard errors.

- Further head-to-head trials are needed to compare (1) nateglinide with all other oral diabetes medications and (2) repaglinide with other oral diabetes medications besides second-generation sulfonylureas.

- More studies should compare one combination of oral diabetes medications directly with another combination (specifically metformin, sulfonylureas, and thiazolidinediones in dual combinations as starting therapy) for all outcomes, as many clinicians have started using combinations as initial treatment in persons with diabetes.

- Further research is needed on the effects of oral diabetes medications on beta cell function over a 3-5 year period or longer, using standardized outcomes, such as c-peptide and insulin levels, and time to requiring insulin.

- A systematic review of drug-drug interactions in subjects with diabetes would help clinicians with treatment decisions.

- Future studies comparing oral diabetes medications must consider any new oral diabetes medications that may be placed on the market, such as the dipeptidyl peptidase IV (DPP-IV) inhibitor sitagliptin, which has just been approved by the Food and Drug Administration.

- Lastly, studies comparing combinations of older diabetes medications, such as sulfonylureas and metformin, with combinations of newer oral diabetes medications, such as thiazolidinediones in

combination with DPP-IV inhibitors or meglitinides, would be interesting, especially given the cost associated with newer oral diabetes medications.

Synopsis

Several clinical trials have investigated short-term outcomes of various preparations of oral medications for type 2 diabetes. Compared to newer medications, such as thiazolidinediones and meglitinides, metformin had similar or superior effects on a range of clinically relevant short-term outcomes. For these same outcomes, second-generation sulfonylureas generally were comparable to thiazolidinediones and meglitinides. In terms of safety, each medication was associated with specific adverse events, although thiazolidinediones and second-generation sulfonylureas were associated with more serious adverse events, such as congestive heart failure and serious hypoglycemia, respectively. Repaglinide may be associated with less serious hypoglycemia in the elderly and in people who skip meals. Lactic acidosis rates were similar for metformin in comparison with other oral diabetes medications. Thus, metformin may be associated with less risk of serious adverse events than second-generation sulfonylureas or thiazolidinediones. When oral diabetes medications were combined, the effects with respect to HbA1c levels and adverse events were generally additive. If each individual drug was used at a lower dose in the combination, fewer adverse events were seen.

Not much evidence exists that might enable one to know a priori which medications are most likely to be effective in identifiable subgroups of patients with diabetes, nor does much evidence exist to predict which particular patients may be most susceptible to the adverse events associated with particular drugs.

Additional information on serious but infrequent adverse treatment effects will have to come from observational studies, particularly case-control studies. Remarkably, we found only one case-control study that qualified for inclusion in this review. Well-done observational studies may also be helpful in elucidating long-term outcomes, although confounding by indication may be difficult to adjust for in such studies.

In the absence of compelling evidence from long-term trials that include assessment of cardiovascular disease outcomes, clinicians should use data on short-term outcomes and safety to guide treatment decisions for oral diabetes medications. Physicians and patients can feel comfortable using older medications such as metformin and second-generation sulfonylureas, as monotherapy or in combination, before newer diabetes medications such as thiazolidinediones or meglitinides, especially when cost is a factor. Future research should focus on comparing combinations of newer medications (DPP-IV inhibitors, meglitinides, and thiazolidinediones) with combinations of older medications (metformin and second-generation sulfonylureas) with respect to long-term effectiveness and safety.

Addendum

Two high-profile original studies and one meta-analysis on this topic have been published since this review was completed.[2,3,4] One 4-year double-blind randomized trial[2] compared rosiglitazone monotherapy with metformin or glyburide monotherapy and showed a significant difference in HbA1c favoring rosiglitazone (between-group absolute difference of -0.42 percent for rosiglitazone vs. glyburide and -0.13 percent for rosiglitazone vs. metformin). However, the incidence of cardiovascular events was lower with glyburide than with rosiglitazone or metformin (1.8 percent, 3.4 percent, and 3.2 percent, respectively; p < 0.05). This effect was mainly driven by significantly fewer congestive heart failure events and a nonsignificantly lower rate of nonfatal myocardial infarction events in the glyburide group. The high loss to followup (40 percent) may account for some differences between groups, since the loss to followup was disproportionate between the groups. This study illustrates the importance of having more long-term followup data on cardiovascular outcomes. At a minimum, clinicians should not assume that a small benefit measured in

[2] Kahn SE, Haffner SM, Heise MA, et al., ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006 Dec 7;355(23):2427-43.

[3] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356. Accessed on May 21, 2007, at www.nejm.org.

[4] Home PD, Pocock SJ, Beck-Nielsen H, et al., RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes–an interim analysis. N Engl J Med 2007. Accessed on June 5, 2007, at www.nejm.org.

terms of HbA1c reduction will be associated with an improvement in cardiovascular outcomes. Indeed, this study suggests that cardiovascular outcomes could be worse with rosiglitazone despite its having a more beneficial effect on HbA1c.

Of note, the fracture rate among women was higher in the rosiglitazone group than in the metformin and sulfonylurea groups (9.3 percent, 5.1 percent, and 3.5 percent, respectively; p < 0.01).[2] We did not find any reported fractures in shorter duration trials, and this will be an important area for future research. For other outcomes reported in this article, the results were similar to those included in our report.

In the meta-analysis,[3] the authors reported that, in comparison with other oral diabetes medications or placebo, rosiglitazone was associated with a borderline-significant increased risk of myocardial infarction (odds ratio, 1.43; 95-percent confidence interval (CI), 1.03 to 1.98) and a nonsignificant association with cardiovascular death (odds ratio, 1.64; 95-percent CI, 0.98 to 2.74). When they analyzed specific drug-drug or drug-placebo comparisons, their results were not statistically significant. Similarly, our report did not find any statistically significant differences between specific oral diabetes medications in cardiovascular outcomes other than congestive heart failure.

The authors acknowledged several limitations of their study: (1) there were small numbers of absolute events; (2) the primary outcomes of the short-term trials were not cardiovascular events; and (3) the authors had no access to original source data. Among additional limitations that influenced their conclusions was their decision to include studies with diverse patient populations. They pooled studies that examined use of rosiglitazone for conditions other than type 2 diabetes, including studies of patients with chronic psoriasis, Alzheimer's disease, type 2 diabetes, and impaired glucose tolerance. Had the authors excluded data from the DREAM trial,[5] which was conducted in adults with prediabetes, the pooled estimate of risk associated with

rosiglitazone would have fallen short of statistical significance. They also included a study in which the patients had a history of congestive heart failure, even though rosiglitazone is currently contraindicated in these subjects. Inclusion of these data may have produced a higher apparent risk than would be expected in practice today. They also excluded six studies that reported no cardiovascular events in either group, thereby biasing their results against finding no difference. Given the limitations of the analysis, the effects of rosiglitazone on cardiovascular mortality and myocardial infarction are still uncertain.

After the release of the meta-analysis on rosiglitazone and cardiovascular risk,[3] an interim analysis of the RECORD study[4] was published. This randomized trial of subjects with uncontrolled type 2 diabetes compared addition of rosiglitazone to existing metformin or sulfonylurea monotherapy vs. the combination of metformin plus sulfonylurea (control group). This analysis yielded a hazard ratio of 1.08 (95-percent CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease after a mean followup of 3.7 years. The hazard ratio was driven by more congestive heart failure in the rosiglitazone group than in the control group (absolute risk, 1.7 percent vs. 0.8 percent). In Kaplan-Meier curves, the risk of 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. One limitation of this interim analysis was the lack of power to detect differences because of lower numbers of cardiovascular events than initially predicted. The RECORD study may now have trouble reaching the desired power for detecting a difference in cardiovascular risk if patients withdraw from the rosiglitazone arm of the study.

Overall, these recent reports are consistent with our review, which found no conclusive evidence of worse cardiovascular morbidity or mortality, outside of the higher risk of congestive heart failure with thiazolidinediones than with other oral medications. These new studies substantiate our call for more vigorous post-marketing surveillance and long-term comparative assessments of major clinical outcomes. For example, such studies should pay attention to the risk of myocardial infarction with rosiglitazone compared with other oral diabetes medications.

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[5] DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006 Sep 23;368(9541):1096-105.

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Summary Table A. Evidence of comparative effectiveness of oral diabetes medications

Key question	Level of evidence[1]	Conclusions
1. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical measures?		
1a. Glycated hemoglobin (HbA1c)	Moderate to high	Most oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, metformin, and repaglinide) had similar absolute reductions in HbA1c (~1%) as monotherapy.
	Low	Indirect data in addition to a few head-to-head trials showed that nateglinide and alpha-glucosidase inhibitors were less efficacious in reducing HbA1c (~0.5-1% absolute difference) compared with other oral diabetes medications.
	Moderate to high	Combination therapies were better at reducing HbA1c than monotherapy by about 1% (absolute difference).
1b. Weight	High to moderate	Metformin consistently caused weight loss (~1-5 kg) when compared with thiazolidinediones, second-generation sulfonylureas, and combinations of metformin plus second-generation sulfonylureas, which generally increased weight.
	Low	Thiazolidinediones and second-generation sulfonylureas caused similar weight gain (~3 kg) when used in monotherapy or combination therapy with other oral diabetes medications.
	Low	Thiazolidinediones caused weight gain (~3 kg) when compared with acarbose and repaglinide based on indirect comparisons of placebo-controlled trials as well as a few direct comparisons.
	Low	Acarbose compared with sulfonylureas showed no 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 when compared with acarbose, which was weight neutral.
	Low	Using a few head-to-head comparisons and indirect comparisons, acarbose had similar weight effects when compared with metformin.
	Moderate	Repaglinide had similar effects on weight when compared with second-generation sulfonylureas. There were too few comparisons of repaglinide with other oral diabetes medications.

Summary Table A. Evidence of comparative effectiveness of oral diabetes medications (continued)

Key question	Level of evidence[1]	Conclusions
1. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical measures? (continued)		
1b. Weight (continued)	Insufficient	There were too few comparisons of nateglinide with any other oral diabetes medication for the effect on weight to draw conclusions.
1c. Systolic and diastolic blood pressure	Moderate to low for most comparisons[2]	All oral diabetes medications had similarly minimal effects on systolic and diastolic blood pressure (<5 mm Hg)
	Insufficient	Too few studies compared meglitinides with other oral diabetes medications besides sulfonylureas to draw firm conclusions.
1d. Low-density lipoprotein (LDL)	Moderate for monotherapy comparisons and moderate to low for combinations compared with monotherapy	Thiazolidinedione monotherapy and rosiglitazone in combination with metformin or sulfonylurea increased LDL (~10-12 mg/dL) compared with metformin or second-generation sulfonylurea monotherapy, which generally decreased LDL.
	Moderate	Rosiglitazone increased LDL more than pioglitazone (~10-15 mg/dL), using indirect comparisons and a few head-to-head comparisons
	Low to very low	Using 1 head-to-head trial and mainly indirect comparisons, rosiglitazone increased LDL more than acarbose (~10-15 mg/dL).
	Moderate	Metformin decreased LDL compared with second-generation sulfonylureas (~10 mg/dL).
	Low	Metformin monotherapy compared with metformin plus a sulfonylurea showed similar effects on LDL.
	Low to very low	Indirect comparisons showed similar effects on LDL when comparing acarbose with metformin. The one direct comparison favored maximally dosed acarbose over submaximally dosed metformin.
	Low	Second-generation sulfonylureas showed similar effects on LDL compared with repaglinide.
	Moderate	The combination of metformin plus sulfonylurea decreased LDL compared with second-generation sulfonylurea monotherapy (~8 mg/dL).
	Low	Alpha-glucosidase inhibitors had similar effects on LDL compared with second-generation sulfonylureas.
	Insufficient	Too few studies compared meglitinides with other oral diabetes medications besides sulfonylureas to draw firm conclusions.
1e. High-density lipoprotein (HDL)	Moderate	Pioglitazone increased HDL more than rosiglitazone, using indirect and a few direct comparisons (~1-3 mg/dL).
	Moderate	Pioglitazone increased HDL compared with metformin or second-generation sulfonylureas (~3-5 mg/dL).

Summary Table A. Evidence of comparative effectiveness of oral diabetes medications (continued)

Key question	Level of evidence[1]	Conclusions
1. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical measures? (continued)		
1e. High-density lipoprotein (HDL) (continued)	Moderate to low	The combination of rosiglitazone with metformin or a second-generation sulfonylurea increased HDL slightly more than metformin or second-generation sulfonylureas alone (~3 mg/dL).
	Moderate to low	Metformin, second-generation sulfonylureas, acarbose, and meglitinides had similarly minimal to no effects on HDL
	Moderate to low	Combination therapy with metformin plus a second-generation sulfonylurea did not differ from monotherapy in effect on HDL with either of the two classes.
1f. Triglycerides (TG)	Moderate	Using indirect comparisons and a few head-to-head comparisons, pioglitazone decreased TG (range 15-52 mg/dL) when compared with rosiglitazone, which increased TG (range 6-13 mg/dL).
	Moderate to low	Pioglitazone decreased TG more than metformin (~26 mg/dL) and showed similar decreases in TG when compared with sulfonylureas. However, the pooled estimate suggested a potential difference when comparing pioglitazone with sulfonylureas of -28.8 mg/dL.
	Low	Indirect comparisons and one direct comparison showed pioglitazone decreased TG more than acarbose (~30 mg/dL).
	Low	Rosiglitazone increased TG when compared indirectly with metformin and acarbose, yet showed similar effects on TG when compared directly with metformin.
	Moderate to low	Metformin decreased TG more than second-generation sulfonylureas and than metformin plus rosiglitazone (~10 mg/dL).
	Moderate to low	Metformin plus a second-generation sulfonylurea decreased TG more than sulfonylurea monotherapy (~30 mg/dL) and showed nonsignificantly decreased TG compared with metformin monotherapy.
	Low to very low	Using indirect and a few direct comparisons, metformin showed similar effects on TG when compared with acarbose.
	Moderate to low	Second-generation sulfonylureas had similar effects on TG compared with repaglinide and acarbose. There were too few comparisons for nateglinide to draw conclusions.
2. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect distal diabetes-related complications of mortality and microvascular and macrovascular outcomes?		
2a. All-cause mortality	Low to very low	It was unclear whether mortality differed when comparing the combination of metformin and a sulfonylurea with sulfonylurea or metformin monotherapy, or when comparing metformin and sulfonylureas.
	Very low	Not enough data existed to compare other oral diabetes medications.

Summary Table A. Evidence of comparative effectiveness of oral diabetes medications (continued)

Key question	Level of evidence[1]	Conclusions
2. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect distal diabetes-related complications of mortality and microvascular and macrovascular outcomes? (continued)		
2b. Cardiovascular disease mortality	Low to very low	It was unclear whether cardiovascular mortality differed when comparing the combination of metformin and a sulfonylurea with sulfonylurea or metformin monotherapy.
	Low to very low	It was unclear whether the effects on cardiovascular mortality differed between metformin and sulfonylureas.
	Very low	Not enough data existed to compare other oral diabetes medications.
2c. Cardiovascular morbidity	Low to very low	There were too few studies to support any conclusions about how cardiovascular morbidity differed between the medications.
2d. Peripheral vascular disease	Low to very low	No evidence existed that showed a difference between oral diabetes medications in effects on peripheral vascular disease.
2e. Microvascular outcomes (retinopathy, nephropathy, neuropathy)	Low to very low	Too few comparisons were made to draw any firm comparative conclusions on microvascular outcomes.
	Low to very low	Pioglitazone showed similar effects on nephropathy compared with sulfonylureas in 3 RCTs lasting less than a year and showed greater improvements in proteinuria when compared with metformin in 2 RCTs lasting less than a year.
3. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to influence other health outcomes, including quality of life and functional status?		
3a. Quality of life and functional status	Very low	Too few studies existed to draw any comparative conclusions.
4&5. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in terms of risk of the following life-threatening and non-life-threatening adverse events?		
4&5a. Hypoglycemia	NA	Second-generation sulfonylureas had a higher percent of subjects with hypoglycemic episodes (range 0-58%) compared with metformin (range 0-21%) or thiazolidinediones (range 0-24%). The absolute risk differences between groups were ~5-10%.
	NA	Using indirect comparisons, metformin (range 0-21%) and thiazolidinediones (range 0-24%) had similar incidence of subjects with hypoglycemia, consistent with the few head-to-head trials.
	NA	Glyburide/glibenclamide had higher incidence of subjects with hypoglycemia (range 0-32%) compared with other second-generation sulfonylureas (range 0-14%). The absolute risk difference between groups was ~2%.
	NA	Repaglinide had similar incidence of subjects with hypoglycemia (range 0-15%) compared with second-generation sulfonylureas (range 7-19%).
	NA	Data were sparse on the comparisons of hypoglycemia between acarbose and other oral diabetes medications and between nateglinide and other oral diabetes medications.

Summary Table A. Evidence of comparative effectiveness of oral diabetes medications (continued)

Key question	Level of evidence[1]	Conclusions
4&5. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in terms of risk of the following life-threatening and non-life-threatening adverse events? (continued)		
4&5a. Hypoglycemia (continued	NA	Combinations of metformin plus sulfonylurea (range 5-58%) and sulfonylurea plus thiazolidinedione (range 6-32%) had higher incidence of subjects with hypoglycemia than metformin (range 0-21%) or sulfonylurea monotherapy (range 2-39%). The absolute risk differences were ~8-14%.
	NA	Combination of metformin plus rosiglitazone had a similar percent of subjects with hypoglycemia (range 1-5%) compared with metformin monotherapy (range 0-2%). No serious events occurred in either group in these RCTs.
4&5b. Gastrointestinal (GI) problems/adverse events	NA	Metformin was associated with a greater percent of subjects with GI adverse events (range 2-63%) compared with thiazolidinediones (range 0-36%) and second-generation sulfonylureas (range 0-32%). The between-group absolute risk differences were ~ 5-15%.
	NA	Metformin monotherapy was associated with more frequent adverse events (range 2-63%) compared with the combination of metformin plus a second-generation sulfonylurea (range 1-35%) or metformin plus thiazolidinediones (17%) if the metformin component was at a lower dose than the metformin monotherapy arm.
	NA	There was a suggestion from a few placebo-controlled and head-to-head trials that metformin and acarbose have a similar incidence of subjects with GI adverse events (range 8-29% vs. 15-30%).
	NA	There was a suggestion from a few placebo-controlled and head-to-head trials that meglitinides have a lower incidence of subjects with GI adverse events (range 8-11%) than metformin (range 8-29%) (between-group absolute differences of ~5-15%).
4&5c. Elevated aminotransferase levels/liver failure	NA	Several oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and metformin) appeared to have similarly low rates (<1%) of clinically relevant elevated aminotransferase levels (>1.5 to 2 times the upper limit of normal or liver failure).
	NA	Insufficient studies evaluated or reported on the effects of meglitinides and acarbose on serum aminotransferase levels, but they appeared to be similar to effects of other oral diabetes medications.
4&5d. Congestive heart failure (CHF)	NA	Thiazolidinediones had greater risk of CHF compared with metformin or sulfonylureas (2 RCTs with absolute between-group risk differences of 1-2%; cohort studies had a range in odds ratios of 1.06-2.27, which was significant in 4 of 5 studies).
	NA	Metformin and second-generation sulfonylureas had similarly little impact on incident CHF.
4&5e. Edema/hypervolemia	NA	Thiazolidinediones had a greater percent of subjects with edema (range 0-26%) than second-generation sulfonylureas (range 0-8%) or metformin (range 0-4%). The range in between-group absolute risk differences was 2-21%. Of note, no cases of macular edema were reported.

Summary Table A. Evidence of comparative effectiveness of oral diabetes medications (continued)

Key question	Level of evidence[1]	Conclusions
4&5. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in terms of risk of the following life-threatening and non-life-threatening adverse events? (continued)		
4&5e. Edema/ hypervolemia (continued)	NA	Data were too sparse to draw conclusions about comparisons of the incidence of edema with other oral diabetes medications.
4&5f. Lactic acidosis	NA	The rate of lactic acidosis was similar between metformin and other oral diabetes medications or placebo (8.4 vs. 9 cases per 100,000 patient-years).
4&5g. Anemia, thrombocytopenia, and leucopenia	NA	Thiazolidinediones may be associated with a greater percent of subjects with anemia (range 3-7%) than other oral diabetes medications (range 2-3%). The absolute between-group differences were ~1-5%.
4&5h. Cancer	NA	There were too few studies and too few cancer cases to draw comparative conclusions.
4&5i. Allergic reactions requiring hospitalization	NA	No serious allergic reactions requiring hospitalization were reported.
4&5j. Withdrawals due to unspecified adverse events	NA	There were no significant differences among oral diabetes medications in withdrawals due to unspecified adverse events.
4&5k. Food and Drug Administration (FDA) data	NA	Pioglitazone was associated with an increased rate of hospitalization for acute cholecystitis compared with placebo in a pooled analysis.
	NA	FDA data were consistent with the adverse event findings reported above.
6. Do safety and effectiveness of oral diabetes medications for the treatment of adults with type 2 diabetes differ across particular adult populations, such as those based on demographic factors (e.g., race/ethnicity, age >65 years, or gender) or comorbidities (e.g., renal insufficiency, congestive heart failure, liver disease, obesity, depression, schizophrenia)?		
	NA	Studies had too few analyses to draw comparative conclusions for this question.

[1] Definitions of levels of evidence: 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; NA = not applicable since there was no validated grading system to determine level of evidence for adverse events.

[2] The evidence was graded very low for the following comparisons related to blood pressure effects: metformin vs. metformin plus sulfonylurea, sulfonylurea vs. sulfonylurea plus thiazolidinedione, meglitinides vs. sulfonylureas, and alpha-glucosidase inhibitors vs. all other oral diabetes medications.

Abbreviations: CHF = congestive heart failure; FDA = Food and Drug Administration; GI = gastrointestinal; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized controlled trial; TG = triglycerides.

Summary Table B. Synopsis of comparative effectiveness of oral diabetes medications

Outcomes	SU vs. Met	SU vs. TZD	SU vs. Meg	Met vs. TZD
HbA1c	ND	ND	ND[1]	ND
Weight	Met	ND	ND[1]	Met
SBP/DBP	ND	ND	Insufficient	ND
LDL	Met	SU	ND[1]	Met
HDL	ND	TZD	ND[1]	TZD
TG	Met	ND[2]	ND[1]	Pio[3]
All-cause mortality	Insufficient	Insufficient	Insufficient	Insufficient
CVD mortality/ morbidity	Insufficient	Insufficient	Insufficient	Insufficient
Peripheral vascular disease	Insufficient	Insufficient	Insufficient	Insufficient
Microvascular outcomes	Insufficient	Insufficient	Insufficient	Insufficient
Quality of life	Insufficient	Insufficient	Insufficient	Insufficient
Hypoglycemia	Met	TZD	ND[1]	ND
GI	SU	Insufficient	Insufficient	TZD
Elevated aminotransferase levels/liver failure	ND	ND	Insufficient	ND
CHF	ND	SU	Insufficient	Met
Edema	Insufficient	SU	Insufficient	Met
Lactic acidosis	ND	Insufficient	Insufficient	ND
Anemia	Insufficient	SU	Insufficient	Met

[1] These conclusions refer to sulfonylurea vs. repaglinide only. See the text for more information about the comparison of sulfonylureas with nateglinide.

[2] Pioglitazone decreased triglycerides, while rosiglitazone increased triglycerides; therefore, pioglitazone showed similar effects on TG when compared with sulfonylurea, while rosiglitazone likely was worse than sulfonylureas but no direct comparisons were available to draw firm conclusions.

[3] Pioglitazone decreased triglycerides, while rosiglitazone increased triglycerides; therefore, pioglitazone was better than metformin, while rosiglitazone was worse than metformin.

Abbreviations: CHF = congestive heart failure; CVD = cardiovascular disease; DBP = diastolic blood pressure; GI = gastrointestinal; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL= low-density lipoprotein; Meg = meglitinides; Met = metformin; ND = no apparent difference; Pio = pioglitazone; SBP = systolic blood pressure; SU = second-generation sulfonylurea; TG = triglyceride; TZD = thiazolidinediones.