Drug Class Review
on
Oral Hypoglycemics

Final Report Update 2

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A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description. Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

In the United States, approximately 16 million persons have type 2 diabetes mellitus. Diabetes is associated with increased morbidity from vascular disease. Hyperglycemia is thought to increase the risk of these vascular complications and, in the United Kingdom Prospective Diabetes Study, intensive treatment with diet, insulin, or oral hypoglycemic medications reduced the risk of microvascular complications by about 25%. While the optimal level of glycemic control is not known, most practice guidelines recommend that pharmacologic treatment be initiated in patients who have a fasting glucose level > 140 mg/dL or a HbA1c value >8% despite efforts at dietary control.

The oral hypoglycemics addressed in this review are listed in Table 1. Sulfonylureas are a class of oral drugs that reduce blood glucose levels by stimulating insulin secretion. The elevated insulin levels reduce hepatic glucose production and increase muscle glucose uptake. First-generation sulfonylureas available in the U.S. include chlorpropamide, tolazamide, and tolbutamide. Second-generation sulfonylureas available in the U.S. are glipizide, glimepiride, and glyburide (also called glibenclamide). An extended release form of glipizide is also available. In the U.S., glyburide is available under several trade names, including Micronase, DiaBeta, and Glynase. Glynase, a micronized form of glyburide, has different dosage and duration of action than the nonmicronized preparations.[1] Because these products are labeled differently by the FDA, for the purposes of this review we considered them different drugs. Two other oral antidiabetic drugs that work by stimulating insulin secretion, repaglinide and nateglinide, are available in the U.S. These drugs have been called "non-sulfonylurea secretagogues."

Table 1. Oral hypoglycemic agents included in this review

Drug	Usual /Maximal Dose And Interval	Duration (Hours)	Active Metabolites
Oral Sulfonylureas			
1st generation			
Chlorpropamide	250-500 mg po qd	24-72	yes
Tolazamide	250-500 mg po bid	12-24	yes
Tolbutamide	500-1500 mg po bid	6-12	no
2nd generation			
Glimepiride	4-8 mg po qd	≥24	yes
Glipizide	10-20 mg po bid	≥24	no
Glyburide	5-20 mg po qd*	16-24	weak
Glyburide micronized	3-12mg po qd	12-24	weak
Non-sulfonylurea secretagogues			
Nateglinide	60-120 mg tid before meals	1.5	yes
Repaglinide	0.5-4 mg bid-qid before meals	1	yes

Source: Drug Facts and Comparisons
*May be split bid above 10 mg/qd

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide committee of experts. Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations

of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Question 1. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbA1C levels?

Key Question 2. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in he progression or occurrence of clinically relevant outcomes?

Key Question 3. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse effects?

Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications, co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one oral hypoglycemic is more effective or associated with fewer adverse effects?

METHODS

Literature Search

We searched the Cochrane Central Register of Controlled Trials (2004, Issue 3), MEDLINE (through September Week 3 2004), EMBASE (through 3rd Quarter 2004), and reference lists of review articles. In electronic searches, we combined terms for and relevant research designs (see Appendix A for complete search strategy). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

We applied the following eligibility criteria to identify eligible articles:

Inclusion criteria:

1. Good-quality and fair-quality studies.
2. The patients were adults with Type 2 diabetes. Subgroups of interest will include, but are not limited to, different races, ages (older adult versus younger adult), and gender.
3. Intervention included either:
    - Sulfonylureas: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide (both immediate and extended release formulations included).
    - Short-acting secretagogues: repaglinide and nateglinide
4. For effectiveness (lowering of HbA1c), study is a fair-or-better-quality systematic review or double-blind, randomized controlled trial (including crossover trials) in an outpatient setting (including emergency department).
5. Clinically relevant outcomes include:
    - Progression or occurrence of microvascular disease (nephropathy as evidenced by proteinuria/dialysis/transplant/end-stage renal disease, retinopathy including proliferative retinopathy and blindness, and neuropathy)
    - Progression or occurrence of macrovascular disease (cardiovascular disease and mortality, myocardial infarction, stroke, coronary disease, angioplasty/CABG, amputation)
    - Other complications of diabetes
    - Quality of life
    - All-cause mortality

To be included, reports about safety or adverse events had to report total withdrawals, withdrawals due to specific adverse events such as hypoglycemia, weight gain, or effects on lipids; or the frequency and severity of these specific adverse events. Controlled clinical trials, longitudinal cohort studies, and drug-drug interaction studies were eligible for inclusion.

When properly designed, direct comparator ("head-to-head") trials provide the best-quality evidence to compare the effectiveness and safety of different drugs. Direct comparator trials were available for some drug-drug comparisons.

Observational studies were eligible for the review of adverse events. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to

minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Exclusion criteria

1. No original data: Paper does not contain original data (e.g., non-systematic review, editorial, letter with no original data).
2. Studies of multiple oral hypoglycemic drugs (e.g., sulfonylurea/metformin) where the effect of the sulfonylurea cannot be delineated.
3. Non-English title and abstract.
4. Article published in abstract form only.

Special note on Ischemic Preconditioning. We did not include studies of the effect of different oral hypoglycemic medications on *ischemic preconditioning*. Because there are no clinical studies comparing the risk of cardiac events among patients taking different oral hypoglycemics, none of the studies concerning ischemic preconditioning met the inclusion for this review. Nevertheless, because the issue is of growing concern among diabetologists, we provide a brief description of the types of studies that are available.

The term *ischemic preconditioning* refers to the ability of a transitory ischemic episode (e.g., angina) to improve tolerance of subsequent ischemic episodes.[2] For example, an angina patient who has a treadmill test, then rests, then has another treadmill test will tolerate more exercise the second time than the first. Similarly, patients who have preinfarction angina may have less myocardial damage after acute MI than patients who do not.

Not all patients have the ischemic preconditioning response. Its absence may indicate a poor prognosis. For example, among patients undergoing percutaneous coronary interventions (PTCA or stents), those who have ischemic preconditioning are at lower risk of death or non-fatal MI by one year.[3]

Diabetics are less likely than other cardiac patients to have an ischemic preconditioning response. It is not clear whether diabetes itself or sulfonylurea use is responsible, but several animal studies and *in vitro* human studies implicate sulfonylureas. Moreover, in human studies, the sulfonylureas differ in their effect on ischemic preconditioning: specifically, glyburide is more likely to block the response than glimepiride.[4-7]

The relation of sulfonylurea use to cardiovascular events, particularly postinfarction mortality, has been debated for over 30 years.[8] The reassuring findings of the UKPDS study (discussed below) greatly reduced but did not eliminate these concerns. For example, in a retrospective analysis of diabetic patients undergoing angioplasty at the Mayo Clinic from 1985 to 1994, diabetics who took sulfonylureas were almost three times as likely to die after PTCA following myocardial infarction than diabetics who did not take sulfonylureas.[9] This study had serious flaws, but it revived interest in ischemic preconditioning as a possible mechanism for the increased risk of postinfarction and post-intervention complications among diabetics.

Experts disagree about the clinical significance of these findings. One editorial, for example, has recommended that use of glyburide be "retired," especially for hospital use.[10] On the other hand, one review of 21 studies concluded:

"in experimental studies the cardiac effects of sulfonylureas differ: both deleterious and protective for glyburide, nil for glimepiride and gliclazide on ischemic preconditioning. In all cases the clinical consequences seem to be nil." A third concluded, "…studies [have] failed to

establish a definite link between sulfonylurea treatment before acute myocardial infarction and in-hospital mortality. However, when the myocardium becomes exposed to repeated or prolonged periods of ischaemia, ischaemic preconditioning may become clinically important. Myocardial ischaemia can also develop during emergency or elective angioplasty and during coronary bypass surgery. Therefore discontinuation of sulfonylurea treatment should be considered in these circumstances."[11]

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[12, 13] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality and were excluded from the review; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis
We summarized our results in evidence tables and in a narrative summary.

RESULTS

Overview
Searches identified 1,456 citations: 630 from the Cochrane Library, 414 from MEDLINE, 347 from EMBASE and 65 from reference lists and pharmaceutical company submissions. We included 12 head to head trials (5 of the 12 trials are from UKPDS), 2 placebo controlled trials, one open trial and one systematic review. Figure 1 details the reasons for study exclusion. Twenty head to head trials were excluded because they did not report any of the outcome measures selected for this review or because of poor- or poor-to-fair quality (internal validity.) (Appendix C) Most of the excluded poor-quality studies were small, did not compare baseline data or had major baseline differences, had high losses to follow-up, or excluded dropouts or nonresponders from the analysis and did not report enough information to calculate intention-to-treat results.

United Kingdom Prospective Diabetes Study
The largest head-to-head trial was the UK Prospective Diabetes Study.[14] Unlike the other studies we found, the UKPDS addressed three of our key questions (glycemic control, outcomes, and adverse events), permitting a more complete comparison of the advantages and disadvantages of the compared drugs. Although it was an open study, it used adequate methods of randomization, was analyzed as an intention-to-treat study, had few dropouts, and examined several important clinical endpoints. Moreover the drugs it compared were not new to the market, reducing the chance of bias due to the lack of blinding.

The UKPDS was designed to address four questions:
- Will improved blood glucose control by increasing insulin supply be beneficial or harmful?
- Will insulin therapy or sulfonylurea therapy be particularly beneficial or harmful?
- Will first- or second-generation sulfonylurea be particularly beneficial or harmful?
- Will improving glucose control by enhancing insulin sensitivity with metformin be beneficial or harmful?

The first two questions are outside the scope of our review, but were examined in a recent, good-quality systematic review conducted for the US Preventive Services Task Force. [15] That review concluded that the UKPDS was the best evidence available to support "intensive treatment" to control blood glucose in patients who have Type 2 Diabetes Mellitus. In the UKPDS, "intensive treatment," or "tight control," refers to a policy of increasing drug therapy to achieve a goal of normal fasting blood glucose levels. The UKPDS found that treatment with a sulfonylurea or insulin over the first 10 years after diagnosis of diabetes decreased the risk of microvascular disease. For all hypoglycemic drugs combined (insulin or a sulfonylurea), intensive glycemic control was associated with a 25% reduction in all *microvascular* endpoints combined, corresponding to a number needed to treat of 42 patients to prevent one event in 10 years. This difference was due primarily to a difference in the risk of having retinal laser photocoagulation (RR for intensive treatment 0.71, NNT=37 to prevent one event over 10 years.)

No other clinical endpoints in the UKPDS reached statistical significance, but intensive treatment improved several intermediate endpoints (progression of retinopathy, proteinuria, two-fold increase in creatinine.) The number needed to treat to prevent one clinical endpoint was 19.6 (CI 10-500). The confidence interval indicates that intense glycemic control for 10 years prevents one or more complications of diabetes for every 10 to 500 patients treated.

The parts of the UKPDS of most interest in this review are described in Table 2 and in Figure 2. The largest, most important part was the UKPDS 33[16] "main randomization" study, which is shown in bold in the figure. Data comparing the effectiveness and safety of first- and second-generation sulfonylureas in patients with FPG > 15 mmol/L, called "primary diet failure randomization" versus the main randomization group was reported in UKPDS 24 (Table 2). UKPDS 34[17] reported separately on 342 overweight patients randomly allocated metformin therapy.

Table 2. UKPDS trial populations relevant to this review

Population	Comparison*	Comment
1.UKPDS 33 "Main randomization" Subjects who had fasting plasma glucose values between 6 mmol/l and 15 mmol/l after 3 months of diet therapy.	Intensive treatment with chlorpropamide vs. glyburide or glipizide or conventional therapy	Stratified by body weight (>20 lb over ideal body weight vs. <20 lbs over) to ensure equal number of obese patients in each group
2. UKPDS 24"Primary diet failure randomization." Subjects who had fasting plasma glucose values above 15 mmol/l despite 3 months of diet therapy.	Intensive treatment with chlorpropamide vs. intensive treatment with glyburide or glipizide.	Stratified by body weight (>20 lb over ideal body weight vs. <20 lbs over) to ensure equal number of obese patients in each group
3. UKPDS 34 "Effect of metformin in overweight patients". Overweight** subjects treated.	Intensive treatment with metformin or sulfonylurea vs. conventional treatment	Supplementary trial of overweight and non-overweight patients failing goals, randomized to continue sulfonylurea or add metformin.

*Insulin was also a comparator

** ≥ 120% of "desirable" body weight (e.g., weights associated with the lowest mortality in the Build and Blood Pressure Study, 1959); ranged by height (in shoes) and frame size (rating of small medium or large by chest width and depth, hip width, bone thickness, muscularity and length of trunk relative to total height)[18]

Main randomization

In the "main randomization" population, 4,209 subjects who had fasting plasma glucose values between 6 mmol/l and 15 mmol/l were randomized to intensive treatment (70%) or to conventional therapy (30%). In patients randomized to intensive treatment, the goal of management was to get the fasting glucose below 6 mmol/l. At the first 15 sites, intensive treatment patients were randomized to insulin, chlorpropamide (up to 500 mg daily), or glyburide (up to 10 mg bid.) At the last 8 sites, patients were randomized to insulin, chlorpropamide or to glipizide (up to 20 mg bid.).

a) Many subjects initially assigned to intensive treatment with a sulfonylurea eventually developed a fasting blood glucose level higher than 6 mmol/l despite maximal doses. Until 1989, these subjects were maintained on monotherapy with the sulfonylurea unless their fasting glucose exceeded 15 mmol/l (if it did, insulin was added). From 1990 on, subjects who had fasting glucose levels ≥6 mmol/l despite maximal sulfonylurea therapy were re-randomized either to continue the sulfonylurea or to add metformin.

b) The goal of conventional treatment was to keep the fasting plasma glucose ≤ 15 mmol/l. If this could not be accomplished after one year or more of diet

alone, the subject was re-randomized to one of the drug therapies, still with the goal of keeping the fasting plasma glucose ≤ 15 mmol/l. Most patients originally assigned to diet alone eventually required drug therapy.

c) *Glycemic control.*

- After 3 years of follow-up, there was no significant difference in HbA1c lowering between patients taking chlorpropamide (-0.4% change in HbA1c) and glyburide (-0.3% change).[14] Fewer chlorpropamide patients required addition of a second drug (9% vs. 13%) but more chlorpropamide patients refused treatment or discontinued due to side effects (13% vs. 7%). As a result, the actual number of patients maintained on their assigned therapy was the same for both drugs (78% vs. 79%).

- After 6 years, there was no significant difference in HbA1c between chlorpropamide (-0.3% change in HbA1c) and glipizide (-0.2% change) in HbA1c.[19]

- At the 10-year follow-up assessment, patients who had been assigned to any intensive treatment (insulin or sulfonylurea) had lower HbA1c levels than conventionally treatment patients (7.0% and 7.9%, p<0.0001). After 10 years the net change in HbA1c was –0.38% for chlorpropamide and +0.11% for glyburide (p=0.008). Note that these results are based on an intention-to-treat analysis: By ten years, most patients in both groups were taking combination therapy (the original sulfonylurea plus metformin) or insulin.

d) *Need for additional therapy.*

- In the first 15 centers, at 6 years of 1305 patients randomized to intensive therapy with a sulfonylurea, 44% were on combination therapy with a second agent (UKPDS 26).[20] No significant difference in HbA1c-lowering between chlorpropamide and glipizide was found. In UKPDS 24, more patients assigned to intensive treatment with chlorpropamide (72%, CI 66% to 77%) were on monotherapy than patients assigned to intensive treatment with glyburide (60%, CI 54% to 66%).

- Fifty-three percent of patients required additional therapy at the last 8 centers (UKPDS 57). More patients assigned to glipizide required additional therapy than chlorpropamide (56% vs. 49%, p=0.28).

e) *Outcomes.*

- The UKPDS investigators also compared outcomes after 10 years of intensive treatment with chlorpropamide (n=619) or glyburide (n=615). No direct comparisons of outcome for chlorpropamide vs. glyburide were statistically significant, but chlorpropamide had less favorable results than glyburide when compared to conventional therapy. For example, compared with conventional therapy, the NNT to prevent any diabetes-

related endpoint was 17 for intensive treatment with glyburide (RR 0.82;0.69-0.97, p=0.018), but it was 57 for intensive chlorpropamide (RR 0.93;0.79-1.99, p=36).

- For the combined microvascular endpoint, the NNT for glyburide vs. conventional therapy was 27 (RR 0.66, CI 0.47 to 0.93, p=0.017), but it was 70 for chlorpropamide vs. conventional therapy (RR 0.86, CI 0.63 to 1.17, p=0.33). Patients assigned to chlorpropamide also did not have the same risk reduction in progression to retinopathy as glyburide or insulin at 12 years (p=0.0056).

- No outcome data have been reported for glipizide.

f) *Adverse events.*

- In the UKPDS (UKPDS 13) intensive treatment group, 13% of chlorpropamide patients refused treatment or discontinued due to side effects, versus 7% of glyburide patients.

- Weight gain and hypoglycemic episodes were significantly raised by any intensive drug treatment. Patients assigned to chlorpropamide gained more weight than those assigned to glyburide. Over 10 years, compared with the conventional therapy group, chlorpropamide patients gained 2.6 kg more (1.6-4.9, p<0.0001); glyburide patients gained 1.7 kg more (0.7-2.7, p<0.001); and insulin patients gained 4.0 kg more (3.1-4.9, p<0.0001).
- Identical proportions of patients had hypertension before entering the study, but after 10 years, chlorpropamide subjects were more likely to be on therapy for hypertension than those taking glyburide (43% vs. 36%, p=0.022). Patients assigned chlorpropamide also had significantly higher systolic and diastolic blood pressure at 6 years (143/82 mm Hg vs. 138/80 mm Hg on other therapies, p<0.001). Adjusting for the difference in mean systolic or diastolic blood pressure by logistic regression analysis did not change this finding.

- In the intention-to-treat population (UKPDS 33), major (severe) hypoglycemic episodes at 10 years with chlorpropamide and glyburide were 1.0% and 1.4%, respectively, compared to 0.7% for diet. Compared with chlorpropamide, glyburide was associated with a higher frequency (16% vs. 21%) and a higher annual rate of hypoglycemic episodes (0.4% for chlorpropamide, 0.6% for glyburide, 0.1% for diet therapy.)

- The UKPDS was designed to re-examine whether intensive treatment increases the risk of cardiac events, as had been reported in an earlier trial for tolbutamide (University Group Diabetes Program UGDP)[21, 22] and in a VA cooperative study of intensive insulin therapy. In the UKPDS, there was no adverse effect of tight control on cardiovascular outcomes.

- For glipizide (UKPDS 57), adverse event data from the UKPDS have not been reported fully. A partial report of glycemic control at six years found no difference in the annual rate of hypoglycemic episodes between chlorpropamide (1.8%) and glipizide (1.4%). Weight gain with chlorpropamide was significantly higher at +4.0 kg compared to glipizide +2.8 kg (p=0.048), but was not significantly different when adjusted for initial weight.

Primary diet failure randomization

UKPDS 24 compared insulin, sulfonylureas, and metformin in patients who had fasting blood glucose levels greater than 15 mmol/l (270 mg/dL) despite up to 3 months of diet therapy. This group comprised 15% of the patients recruited, and would have been excluded from most clinical trials. A partial report of the results of this part of the UKPDS 24 was published in 1998.[23]

- By 6 years, 62% of patients assigned to chlorpropamide and 69% patients assigned to glyburide required additional therapy (addition of metformin, addition of insulin, or change to insulin.)

- More major hypoglycemic episodes occurred in this population than in the "main randomization" population. By 6 years, the annual rate of serious (major) hypoglycemic episodes was 2.5% (0.0-6.7) for glyburide and 1.5% (0.0-2.6) for chlorpropamide.

Key Question 1. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbA1c levels?

Head-to-head trials

There was a great gap in quality and relevance between the UK Prospective Diabetes Study and the other seven head-to-head trials that assessed effectiveness, summarized in Table 3 and in Appendix D. Although the studies varied in baseline plasma glucose levels, prior treatments, and length of follow-up, the results were consistent: there was a small absolute change in HbA1c with these agents, only apparent after at least 8 weeks of therapy, and diminishing in time. There were no significant differences in 7 of the 8 trials that followed patients for 15 months or less. The non-sulfonylurea secretagogue repaglinide was found to be superior to glipizide in one fair study,[24] but the dosage of glipizide was maximized at 15 mg, while it is labeled for use up to 40mg. Additionally, only 50% of patients received the 15 mg dose.

We did not identify any trials comparing the first-generation sulfonylureas tolazamide and tolbutamide to other sulfonylureas or to non-sulfonylurea secretagogues

Table 3. Fair- or better quality head-to-head trials.

Trial Drug	Trial Design	Length	Difference in effectiveness measure (HbA1c)	Rating
Glyburide or glipizide vs. chlorpropamide				
UKPDS 13 chlorpropamide or glyburide vs. diet, insulin, metformin, or add-on 1995 British Medical Journal UKPDS 57 chlorpropamide or glipizide vs. diet, insulin, or add-on. 2002 Diabetes Care UKPDS 33 1998 Lancet	Newly diagnosed Type 2 DM 3 month diet run-in, at first 15 centers 2520 patients randomized Last 8 centers, randomized 1027 patients Outcome data on first 15 centers	3 years 6 years 10 years	Chlorpropamide-0.4%, Glyburide -0.3% (NS) Chlorpropamide -0.3% Glipizide -0.2% (NS) Chlorpropamide -0.38% Glyburide +0.11 % (p<0.0001)	Good
Micronized glyburide vs. glyburide				
Carlson 1993 Clinical Therapeutics[1]	Type 2 DM on glyburide > 1 month no washout, 206 patients randomized to continue glyburide or take micronized glyburide	8 weeks	Micr. Glyburide +0.3% Glyburide -0.1% NS	Fair
Glipizide vs. glyburide				
Kitabchi[25] 2000 American J Medical Sciences	Type 2 DM unresponsive to diet, 2-month washout, 18 patients randomized	15 months	Glipizide -1.0% Glyburide -1.3% NS	Fair
Glimepiride vs. glyburide				
Draeger [26] 1996 Horm.Metab.Res.	Type 2 DM on glyburide >2months, 2-week run-in, 1044 patients randomized	12 month	Glimepiride +0.3% Glyburide +0.3% NS	Fair
Repaglinide vs. glyburide				
Landgraf[27] 1999 Eur J Clin Pharm	Type 2 DM on sulfonylurea 1-2 week washout, 194 patients treated	10 week	Repaglinide -0.1%, Glyburide -0.2% NS	Fair
Wolffenbuttell (**micronized)** 1999 Diabetes Care[28]	Type 2 DM diet or OH, 1-week washout, 424 patients randomized, 320 completed it. Higher dropout rate in the glyburide group.	12 month	Repaglinide -0.3%, Glyburide -0.4% NS	Fair, high dropout rate
Repaglinide vs. glipizide				
Madsbad[24] 2001 Diabetic Medicine	Type 2 DM requiring diet or oral hypoglycemic drug, 1-week washout, 256 patients randomized. Did not use maximal doses of glipizide.	12 month	Repaglinide +0.2%, Glipizide +0.8% p<0.05	Fair
Repaglinide vs. glimepiride				
Derosa[29] 2003 Clinical Therapeutics	Type 2 DM requiring diet only, 4-week washout, 132 patients randomized, 124 completed.	12 month	Repaglinide –1.2 Glimepiride –1.1 NS	Fair

Placebo-controlled trials

One fair-quality systematic review compared oral hypoglycemic drugs in type 2 diabetics.[30] It included 63 trials of oral agents, most of which were comparisons to placebo rather than direct comparator trials. The authors found no difference in the effectiveness within or between the sulfonylureas and the non-sulfonylurea secretagogues.

Key Question 2. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the progression or occurrence of clinically relevant outcomes?

Only the UKPDS provides head-to-head evidence on this question, and only for the comparison of chlorpropamide to glyburide. The results of the UKPDS are discussed above.

Repaglinide significantly improved treatment satisfaction and had no effect on well-being or health status after 16 weeks in a 2003 fair quality, placebo-controlled trial of pharmacotherapy-naïve patients with type II diabetes (n=253) (see Appendix E Tables 1 and 2).[31]

Key Question 3. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse events?

Adverse Events

The UKPDS provides the best available data on adverse effects of long-term use of chlorpropamide compared with glyburide and glipizide. Results of the UKPDS were described above.

There are no comparable data for other sulfonylureas or for the newer secretagogues. There were no significant differences in weight and lipid changes in the other head-to-head trials (Table 4), except for a small difference in HDL. One trial found a slight increase in HDL-C. A recent fair-quality systematic review (did not assess quality of included studies) evaluated the effects of different oral agents for diabetes (including sulfonylureas and short-acting secretagogues) on lipid profiles.[32] It included only placebo-controlled trials and uncontrolled studies reporting postexposure changes in lipid status. It found no significant changes in lipid profiles associated with any of the drugs included in this report.

Table 4. Adverse events in head-to-head trials

TRIAL	ADVERSE EVENTS AND HYPOGLYCEMIA	WEIGHT	LIPIDS
Carlson 1993 Clinical Therapeutics *Glyburide (Gly) vs. Micronized Glyburide (Mic Gly)*	Any adverse event: 61% (no difference) hypoglycemia: Mic Gly 0.9%; Mic 0.9%	NS change	NS change
Kitabchi 2000 American J Medical Sciences *Glipizide (Glip) vs. Glyburide(Gly)*	Any adverse event: NS difference Hypoglycemia: NS difference Severe hypoglycemia: Glip=0 episodes; Gly=0 episodes	NS change	NS change
Draeger 1996 Horm.Metab.Res. *Glimepiride (Gli) vs. Glyburide (Gly)*	Any adverse event: Gli 17%, Gly 19% Hypoglycemia: Gli 11%, Gly 14%	NS change	NS change
Wolffenbuttell 1999 Diabetes Care *Repaglinide (Rep) vs. Micronized Glyburide (Mic Gly)*	Any adverse event: 14% Withdrawals: Total: 25% Hypoglycemia: Rep 9%; Mic Gly 9%	NS change	NS change
Landgraf 1999 Eur J Clin Pharm *Repaglinide (Rep) vs. Glyburide (Gly)*	Hyperglycemia: Rep=13 episodes; Gly=9 episodes Hypoglycemia: 35 episodes overall; Rep 9.5%,Gly 8.9% (p-value NS) Withdrawals: Total 15% Adverse event: 3% overall; Rep 12%, Gly 23%	NS change	NS change except >HDL-C in Rep (1.15 vs.1.11 mmol/L, p=0.005)

TRIAL	ADVERSE EVENTS AND HYPOGLYCEMIA	WEIGHT	LIPIDS
Madsbad 2001 Diabetic Medicine *Repaglinide (Rep) vs. Glipizide (Glip)*	Severe hypoglycemia: Rep=0 episodes; Glip=0 episodes Hypoglycemia: 15%rep 19%gly Other adverse events: 11% overall; Rep 11%, Glip 11% Withdrawals: Adverse events: 26% overall	NS decrease	NS changes

Drug Interactions

We did not identify head-to-head comparative studies of drug interactions. Open label, crossover studies of healthy adults[33] found that the action of repaglinide increased when administered concomitantly with ketoconazole and decreased with rifampicin. Additionally, incidence of hypoglycemic events increased when repaglinide was administered concomitantly with simvastatin or nifedipine. Information about drug interactions from trials in healthy volunteers is described in the package inserts for each drug. Some clinically significant drug interactions are described below in Table 5.

Table 5. Clinically significant drug interactions*

PRECIPITANT DRUG	AFFECTED DRUG	ACTION
Acarbose, alcohol**, monoamine oxidase inhibitors, metformin, salicylates	sulfonylureas	Intrinsic hypoglycemic activity
Chloramphenicol, warfarin	sulfonylureas	Decreased hepatic metabolism
Clofibrate, salicylates, sulfonamides, warfarin	sulfonylureas	Displacement from plasma protein
Monoamine oxidase inhibitors, tricyclic antidepressants	sulfonylureas	Mechanism unknown
Probenecid, salicylates	sulfonylureas	Decreased renal excretion
Nateglinide	CYP2C9 metabolized agents	Nateglinide is a cytochrome P450 isoenzyme CYP2C9 inhibitor
Inhibitors or inducers of cytochrome P450 CYP3A4 isoenzyme	Repaglinide	may increase or decrease repaglinide action

*Adapted from Facts and Comparisons

**Alcohol may cause a disulfiram-like reaction with chlorpropamide

Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications, co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one oral hypoglycemic is more effective or associated with fewer adverse effects?

Demographics

Cross-sectional data reveal important differences among racial groups in the presentation and course of diabetes.[15] However, there is no direct evidence that any sulfonylurea or non-sulfonylurea secretogogue has an advantage in effectiveness for any racial group. In placebo-controlled trials presented to the FDA during the approval process for glimepiride, no differences were found in the antihyperglycemic effect between whites (n = 536), blacks (n = 63), and Hispanics (n = 63) who had Type 2 diabetes. Similarly, in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect of repaglinide was comparable between Whites (n=297) and African-Americans (n=33). Repaglinide had similar pharmacokinetics in Whites (n=74) and Hispanics (n=33). Pharmacokinetic data on nateglinide found no differences among several races and ethnic groups. Glimepiride did not cause significant adverse events in a

2003 placebo-controlled trial[34] in Mexican American patients (n=70) with type II diabetes (see Appendix E Tables 1 and 2). This analysis did not include 10 (20%) patients that dropped out of the study (primary reason "loss to follow-up"). Potentially inadequate randomization methods, suggested by higher mean body weight in the glimepiride group, exclusion of an intention-to-treat analysis, and high attrition (20%) led to a rating of poor quality for this study.

Old age is a risk factor for serious hypoglycemia.[35] An observational study attempted to make the case that longer-acting sulfonylureas were associated with a higher risk of suffering hospitalization for hypoglycemia.[36] Specifically, the authors noted that, at a time when 23.5% of the population with Type 2 diabetes took a long-acting drug, over 40% of hospitalizations due to hypoglycemia were associated with long-acting drugs[36] In the UKPDS trial, however, patients assigned to chlorpropamide had fewer hypoglycemic events than those taking glyburide. In another trial, glipizide and glyburide did not differ in effectiveness or adverse events in an elderly population[37]

Comorbidities

Obesity is common among diabetic patients. In a trial of *conventional versus intensive therapy in overweight patients* (UKPDS 34), a secondary analysis of intensive metformin treatment suggested a significantly lower risk of any diabetes-related endpoint than other sulfonylurea or insulin intensive therapy or conventional therapy. The data also suggested overweight metformin-treated patients had a lower risk of diabetes-related death than conventional therapy, with no difference compared to other intensive therapies; as well as a greater risk reduction in all-cause mortality than conventional or other intensive therapies. Lastly, the data suggested the overweight metformin-group had a lower risk of macrovascular disease than conventional therapy, but no different from other intensive therapies. Conversely, in a subgroup of overweight and non-overweight patients in the *main randomization group,* an increased risk of diabetes related death was suggested with sulfonylurea plus metformin compared to sulfonylurea alone. However, in the combined analysis of the 2 trials, the effects on macrovascular outcomes were not seen.

Renal insufficiency

Repaglinide product information currently recommends initial dose adjustment (0.5 mg) and careful titration in patients with renal insufficiency. These recommendations were based on results of single-dose and steady-state pharmacokinetics studies suggesting increased repaglinide action in this population. More recently, however, an open trial of repaglinide[38] found that rates of glycemic control, hypoglycemia, serious adverse events and deaths were similar for groups of type 2 diabetic patients with normal (n=151) and mild-moderately impaired (n=108) renal functioning and those with severe-extreme renal impairment (n=22), fewer of which reached the highest dose level. It was concluded that repaglinide can be safely titrated according to manufacturer's recommendations in type 2 diabetic patients with any degree of renal impairment.

SUMMARY

Table 6. Summary of the evidence

Key Question	Overall Quality of the Evidence*	Conclusion
1:Comparative Effectiveness For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbA1c levels?	Chlorpropamide vs. glyburide or glipizide: Good. Glimeripide vs. glyburide or glipizide: Fair Repaginide vs. Glyburide or glipizide: Fair Nateglinide, Tolazamide, or tolbutamide vs. others: Poor	Good quality evidence that chlorpropamide and glyburide or glipizide are similar in lowering HbA1c, with a small advantage for chlorpropamide. There is fair-quality evidence that repaglinide, glimepiride, glipizide, and micronized glyburide are similar in effectiveness to glyburide at equivalent doses. There is no reliable evidence comparing tolbutamide, tolazamide, or nateglinide to other drugs in the class.
2: Progression/ occurrence of outcomes For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the progression or occurrence of clinically relevant outcomes?	Chlorpropamide vs. Glyburide: Good Others: no data	There is good evidence from one trial that chlorpropamide is inferior to glyburide in reducing the progression to retinopathy, irrespective of HbA1c. There are not yet any outcome data on other sulfonylureas or non-sulfonylurea secretatogues, but outcome data from the UKPDS on glipizide may still be reported.
3: Safety/Adverse Effects For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse effects?	Chlorpropamide vs. glyburide or glipizide: Good. Glimepiride vs. glyburide or glipizide: Fair Repaginide vs. Glyburide or glipizide: Fair Nateglinide, Tolazamide, or tolbutamide vs. others: Poor	In 1 good-quality long-term trial, chlorpropamide was associated with a lower rate of hypoglycemic episodes that glyburide but was associated with more weight gain and higher blood pressures than glyburide. Glipizide was found to have a similar annual rate of hypoglycemic episodes and weight gain as chlorpropamide. There is fair evidence that glyburide is similar to micronized glyburide, glimeripide, glipizide, and repaglinide with respect to effects on weight and blood pressure. There is no reliable evidence comparing tolbutamide, tolazamide, or nateglinide to other drugs in the class.
4: Subgroups Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications, co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one oral hypoglycemic is more effective or associated with fewer adverse effects?		All of the 2nd generation sulfonylureas and the non-sulfonylurea secretogogues have been shown to have similar effectiveness and safety in men and women and in people of different races or ethnicity. We did not identify evidence that one of the included drugs has an advantage over others in any demographic group, in obese diabetics, or in patients who have a history of hypoglycemic episodes.

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Figure 1. Results of search and selection of included articles

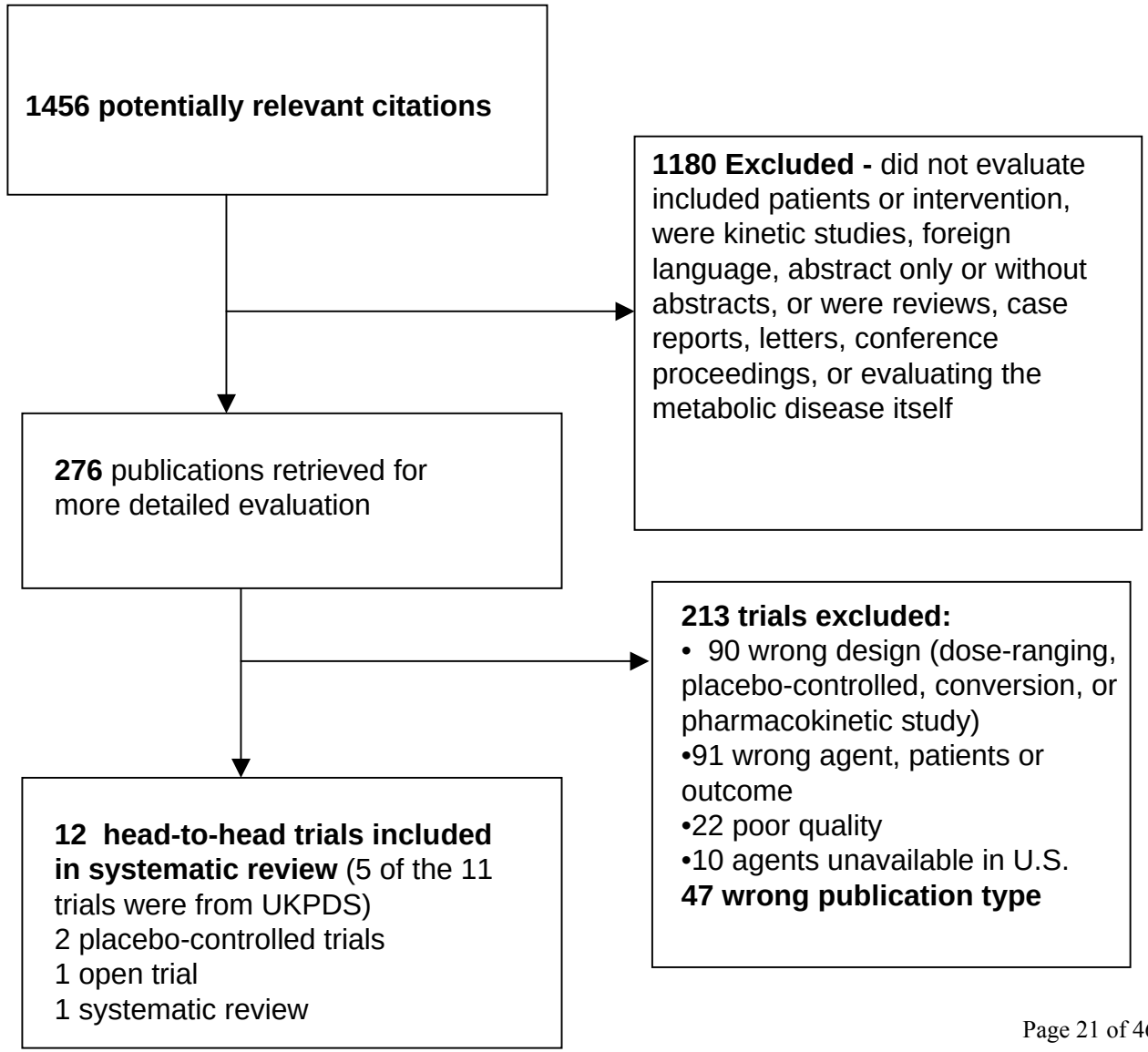

Figure 2. UKPDS trial design

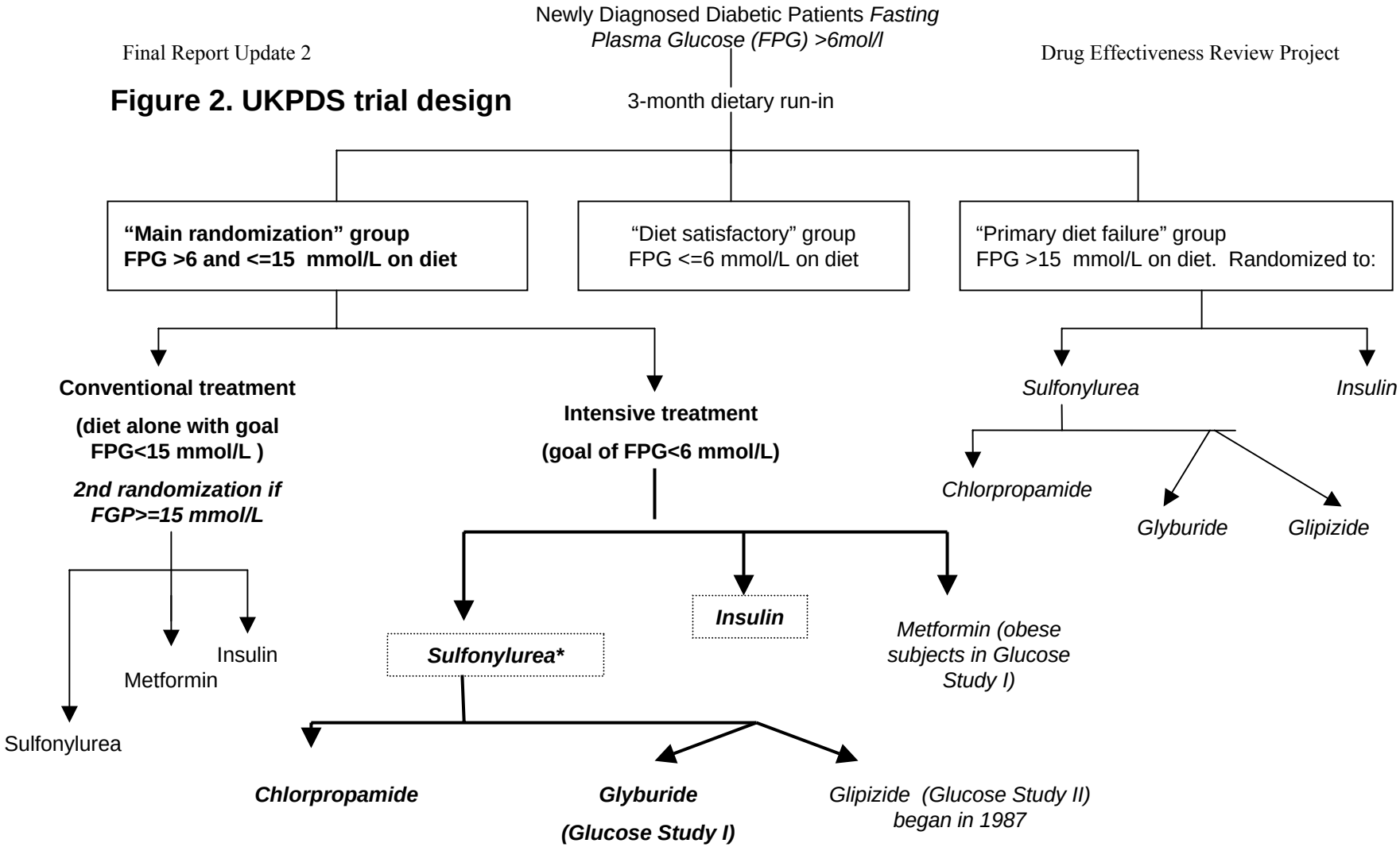

Diagram based on information in UK Prospective Diabetes Study Group, "UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress, and performance." *Diabetologia (1991).34:877-890.*
*Until 1989, sulfonylurea alone was used even if the FPG rose to 15 mmol/L; above 15 mmol/L, metformin was added. From 1990 on, patients taking a sulfonylurea were re-randomized to add metformin for FPG>6 mmol/L or to continue Sulfonylurea alone until FPG rose above 15 mmol/L.

Appendix A. Search Strategy

```
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd
Quarter 2004>
Search Strategy:
--------------------------------------------------------------------------------
1     hypoglycemic agents.ti.
2     sulfonylurea$.ti.
3     acetohexamide.ti.
4     carbutamide.ti.
5     chlropropamide.ti.
6     glicazide.ti.
7     glyburide.ti.
8     tolazamide.ti.
9     glibenclamide.ti.
10     glipizide.ti.
11     glimepiride.ti.
12     nateglinide.ti.
13     fastic.ti.
14     sdz djn 608.ti.
15     senaglinide.ti.
16     starlix.ti.
17     starsis.ti.
18     "ym 026".ti.
19     repaglinide.ti.
20     nn 623.ti.
21     1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or
14 or 15 or 16 or 17 or 18 or 19 or 20
22     diabetes.mp.
23     21 and 22
24     from 23 keep 1-425
```

```
Database: Ovid MEDLINE(R) <1996 to September Week 3 2004>
Search Strategy:
--------------------------------------------------------------------------------
1     exp Diabetes Mellitus, Type II/ or type-2 diabetes.mp.
2     gliclazide.mp. or exp GLICLAZIDE/
3     glibenclamide.mp. or exp Glyburide/
4     glybenzcyclamide.mp.
5     fastic.mp.
6     mitiglinide.mp.
7     senaglinide.mp.
8     starlix.mp.
9     starsis.mp.
10     chlorpropamide.mp. or CHLORPROPAMIDE/
11     glimepiride.mp.
12     glipizide.mp. or exp GLIPIZIDE/
13     glyburide.mp. or exp GLYBURIDE/
14     tolazamide.mp. or exp TOLAZAMIDE/
15     tolbutamide.mp. or exp TOLBUTAMIDE/
16     repaglinide.mp.
17     nateglinide.mp.
18     agee-623.mp. [mp=title, original title, abstract, name of substance,
mesh subject heading]
```

```
19     hoe-490.mp. [mp=title, original title, abstract, name of substance,
mesh subject heading]
20     2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or
15 or 16 or 17 or 18 or 19
21     1 and 20
22     administration, oral.mp. [mp=title, original title, abstract, name of
substance, mesh subject heading]
23     oral$.mp.
24     22 or 23
25     21 and 24
26     limit 25 to human
27     (20031$ or 2004$).ed.
28     26 and 27
29     from 28 keep 1-53
```

```
Database: EMBASE Drugs & Pharmacology <3rd Quarter 2004>
Search Strategy:
--------------------------------------------------------------------------------
1     exp Non Insulin Dependent Diabetes Mellitus/ or type-2 diabetes.mp.
2     chlorpropamide.mp. or exp CHLORPROPAMIDE/
3     glimepiride.mp. or exp GLIMEPIRIDE/
4     glipizide.mp. or exp GLIPIZIDE/
5     glyburide.mp. or exp Glibenclamide/
6     tolazamide.mp. or exp TOLAZAMIDE/
7     repaglinide.mp. or exp REPAGLINIDE/
8     nateglinide.mp. or exp NATEGLINIDE/
9     gliclazide.mp. or exp GLICLAZIDE/
10     glybenzcyclamide.mp.
11     fastic.mp. or exp Nateglinide/
12     mitiglinide.mp.
13     exp Nateglinide/ or senaglinide.mp.
14     starlix.mp. or exp Nateglinide/
15     starsis.mp. or exp Nateglinide/
16     agee-623$.mp.
17     hoe-490.mp.
18     tolbutamide.mp. or exp TOLBUTAMIDE/
19     glibenclamide.mp. or exp GLIBENCLAMIDE/
20     2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or
15 or 16 or 17 or 18 or 19
21     1 and 20
22     oral administration.mp. or exp Oral Drug Administration/
23     po.fs. or oral.tw.
24     22 or 23
25     21 and 24
26     limit 25 to human
27     limit 26 to english language
28     26 not 27
29     limit 28 to abstracts
30     27 or 29
31     (randomised clinical trial$ or randomized clinical trial$).mp.
32     Clinical Trial/
33     Crossover Procedure/
34     (crossover trial$ or cross over trials$).mp.
35     cohort studies.mp. or exp Cohort Analysis/
```

```
36     (observational stud$ or retrospective stud$ or comparative stud$).mp.
37     exp Retrospective Study/
38     exp Comparative Study/
39     31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40     30 and 39
41     from 40 keep 1-397
```

Appendix B. Quality Assessment Methods for Drug Class Reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

   A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

   This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Bandisode 1975 Horm Met Res	1. Washout period, then randomized, double-blind controlled trial of glipizide (n=20) vs. chlorpropamide (n=20) with 18 months of followup. 2. Eligibility: Type 2 diabetics previously treated with diet, insulin, or an oral hypoglycemic agent other than chlorpropamide 3. Maximum dose: glipizide—25 mg/day chlorpropamide—750 mg/day	No eligible outcome measures were reported.	N/A
Prosser 1985 Am J Med Sciences	1. Single-blind randomized trial of glyburide (n=11) vs. chlorpropamide (n=8) with 16 weeks of followup. 2. Eligibility: .Newly diagnosed diabetics 18-65 years who failed diet alone.	No eligible outcome measure (main outcome measure was mean 24 hour glucose level.) Also, poor-quality because of no baseline data, no information about attrition or intention-to-treat.	N/A
Sonksen 1981 Diabetologia Sonksen 1984 Diabetes Care	1. 4-week diet therapy then single-blind crossover trial of glyburide vs. chlorpropamide. 31 patients were randomized. 2. Eligibility: Newly diagnosed diabetics 18-65 years who failed diet alone. 3. Maximum dose: glipizide—25 mg/day chlorpropamide—750 mg/day	No eligible outcome measures. Also, dropouts (33%) were not included in analysis.	N/A
Berelowitz 1994	1. Multicenter randomized 16-week crossover dose-finding trial of 5, 20, or 40 mg sustained-release glipizide vs. glipizide with 40-day followup. 132 patients were randomized. 2. Eligibility: Type 2 diabetics previously treated with glipizide or glyburide 3. Dose based on previous doses of glyburide or glipizide.	Ineligible outcome measure (HgbA1c after 8 weeks.) 123 of 132 patients included in efficacy analysis (not intention-to-treat.) Inadequate baseline information to determine adequacy of randomization.	No difference in Hgb A1c at 8 weeks. Fasting blood glucose levels were lower after sustained-release glipizide for the subgroup of subjects who had FBG>11 mmol/L after 8 weeks of immediate-release glipizide.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Chung 2002	1. Open, randomized crossover trial of sustained-release glipizide vs. glipizide with 40-day followup. 25 patients were randomized. 2. Eligibility: Men 42-71. Inclusion criteria unclear.	Short-term study with no eligible outcome measures.	N/A
Birkeland 1994 Diabetes Care Private/public grants and pharmaceutical company tablets	1. Washout period, then stratified by Hgb A1c, duration of diabetes, age, and body mass index, then randomized, double-blind trial of glipizide vs. micronized glyburide vs. placebo with 15 months of followup. 46 patients. 2. Eligibility: Type 2 diabetics with prestudy HgbA1c between 7% and 11%. 3. Maximum dose: glipizide—15 mg/day micronized glyburide—8 mg/day r (strat), db,pc Type 2 DM on diet, 46 pts included, diet only A1C 7-11%, identical tablets, stratified by baseline characteristics 3-6 mo diet run-in placebo, glyb 1.75 mic=3.5 US, glip 2.5 mg adj wkly by 2.5 mg to FBG < 8mM and Hb,7.5, f/u 3 mo, with Hb>11 withdrawn 12 months 59.yo, 48% men, DM 3.5 yrs, BMI 26.4 kg/m2	No eligible outcome measures (only mean HgbA1c for groups was reported.) The number of patients in each group was unclear, no baseline comparison data was provided, and 6 patients were excluded from the efficacy analysis.	No difference in mean HgbA1c after 15 months. No adverse event data.
Blohme 1979 Acta Med Scand	1. Randomized, double-blind, double-dummy crossover trial of glyburide (n=20) vs. glipizide (n=20) with one year of followup. 2. Eligibility: Asymptomatic Type 2 diabetics with fasting S-glucose despite therapy with 15 mg of glyburide or glipizide. 3. Maximum dose: glimeripide—16 mg glyburide—20 mg (up to 15 mg once or 10 mg bid) Glipizide vs. glyburide,db,dd, crossover,40 pts,4-6 wksx2	No eligible outcome measures.	Unusual design—really 2 trials designed to test the efficacy of switching sulfonylureas.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Dills 1996 Horm. Met. Res	1. Washout period, then randomized, double-blind controlled trial of glyburide (n=288) vs. glimeripide (n=289) with one year of followup. 2. Eligibility: 30-80 year old Type 2 diabetics previously treated with diet or with an oral hypoglycemic agent 3. Maximum dose: glimeripide—16 mg glyburide—20 mg (up to 15 mg once or 10 mg bid)	Fair-poor quality: about 15% of patients did not finish the study, including 39 because of lack of efficacy. The efficacy analysis excluded these patients.	No difference in HbgA1C at 16 or 52 weeks No difference in overall rate of adverse events. Glyburide had more hypoglycemic episodes in the first month, but the difference wasn't statistically significant by 12 months (glyburide—17%, glimeripide—12%, p=0.07)
Groop 1985 Eur J Clin Pharm	1. Randomized double-blind crossover trial of glyburide 10 mg vs. glipizide 10 mg (total n=15) 2. Eligibility: not clear. All were Type 2 diabetics previously treated with an oral hypoglycemic drug., usually glyburide.	No eligible outcome measures.	N/A
Jaber 1990	1. 2-week washout period, then randomized, double-blind crossover trial of glyburide vs. glipizide with 16 weeks of followup. 30 patients were randomized 2. Eligibility: Type 2 diabetics previously treated with diet, insulin, or an oral hypoglycemic agent. 3. Maximum dose: glipizide—40 mg/day glyburide—40 mg/day	Poor-quality: only 19 of 30 subjects completed the study. The dropouts were excluded from the efficacy analysis. Baseline data were reported inadequately; baseline HgbA1c was 13.2 in the glyburide group and 12.4 in the glipizide group.	Final HgbA1c: glyburide 11.1 ± 0.7 glipizide 12.7 ± 1.0 p=0.06
Kilo 1988 Clin Ther	1. Multicenter randomized, open-label dose-finding trial of glyburide vs. glipizide with 3 months of followup. N=109 2. Eligibility: Type 2 diabetics previously well-controlled with tolbutamide, chlorpropamide, or glyburide. 3. Maximum dose: glipizide—40 mg/day glyburide—20 mg/day	No eligible efficacy measures. Inadequate description of baseline characteristics. There was no intention-to-treat analysis for efficacy (103 of 109 included in the analysis.) "Interim analysis"—final results were never reported.	The study was not designed to compare the efficacy of the 2 drugs. Rather it compared their potency. Adverse events: no difference.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Kilo 1992	1. Multicenter randomized, open-label dose-finding trial of glyburide (n=17) vs. glipizide (n=17) with 3 months of followup. 2. Eligibility: Type 2 diabetics previously well-controlled with tolbutamide or chlorpropamide. 3. Maximum dose: glipizide—40 mg/day glyburide—20 mg/day	Poor-quality because 1) open-label study in which there was a high potential for bias in titrating therapy 2) the efficacy analysis excluded 8 of 34 subjects.	Similar rates of adverse events.
Klose Frederiksen 1982 Current Ther Res	1. Rrandomized, double-blind crossover trial of glyburide (n=18) vs. glipizide (n=20) with 8 months of followup. 2. Eligibility: Type 2 who could not be controlled with diet alone, all had been on sulfonylureas. 3. Maximum dose: glipizide—20 mg glyburide—20 mg 38 pts, 8 mo.	No eligible efficacy measures and no individual-level results. Baseline characteristics not described adequately. Method for assessing adverse events not stated.	
Rosenstock 1993	1. Washout period, then open multicenter randomized trial of glyburide (n=70) vs. glipizide (n=69) with a titration phase and maintenance phase. Total followup time was 4 months. 2. Eligibility: Type 2 diabetics 65 years or older who had been well-controlled with a sulfonylurea	Poor-quality. Differential loss to followup: 21.4% of glyburide patients and 43.5% of glipizide patients did not complete the study. Only subjects who completed the study were included in the efficacy analysis.	After 4 months there were no differences in Hgb A1c or in adverse events.
Simic 1991 Southern Med Journal	1. 8-week period of previous therapy with glyburide (n=16) or glipizide (n=10), then changed to the other drug, titrated, then followed for 8 more weeks. 2. Eligibility: Type 2 diabetics who had a fasting blood glucose level greater than 8.3 mmol/L (150 mg/dL) on glyburide or glipizide	Ineligible: pre-post design, not randomized or blinded, no eligible outcome measures.	Designed to test the efficacy of switching from sulfonylurea to another. Fasting blood glucose levels did not improve after switching from glyburide to glipizide or from glipizide to glyburide.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Damsbo 1999 Diabetes Care	1. Double-blind randomized trial of repaglinide (n=42) vs. glyburide (n=41). After titrating the medication dose, patients who had fasting blood glucose levels 110-180 entered the 3-day study 2. Type 2 diabetics aged 40-75, most had been treated with sulfonylureas.	No eligible outcome meaures. 25 glyburide patients and 17 repaglinide patients were included in the analysis, but all were included in the safety analysis	Unusual design to test the effect of accidental dietary noncompliance by giving well-controlled diabetics 2 instead of 3 meals. There were more adverse events in the repaglinide patients (9/42) than in glyburide patients (5/41). Their severity was measured but not reported. There were 4 episodes of symptomatic hypoglycemia in the glyburide patients after the skipped meal, but none in the repaglinide group. There were no differences in the frequency of low blood glucose.
Marbury 1999 Diab Res & Clin Pract	1. One-year multicenter randomized double-blind trial of repaglinide (n=383) vs. glyburide (n=193). 2. Eligibility: Type 2 diabetics 37-75 years old, most previously treated with oral hypoglycemics. 3. Maximum dose: glyburide—15 mg/day repaglinide—12 mg/day	Fair-poor quality. Only 331 of 576 (57%) completed the study; efficacy analysis was not by intention-to-treat, but adverse event analysis was.	No difference in Hgb A1c at 1 year. Adverse events any: repaglinide 30% glyburide 28% hypoglycemia: repaglinide 15% glyburide 19%
Wolffebuttell 1993 Eur J Clin Pharm	1. Open randomized blocks, not concealed, double-blind controlled trial of glyburide (n=15) vs. repaglinide (n=29) with 12 weeks of followup. 2. Eligibility: unclear, most had been taking glyburide 3. Maximum dose: repaglinide —4 mg glyburide—15 mg	Poor-quality. Allocation not concealed, inadequate baseline data, some baseline differences (body weight), and open design in subjects who had taken one of the study drugs.	No difference in Hgb A1C or weight.

Appendix C. Excluded head-to-head trials

Author Year Journal	Characteristics	Reason for exclusion	Results
Ginier 1985 American Journal of Medicine suppl VA/NIH/Upjohn	1. Washout period, then 2-week admission, then randomized to glyburide once daily (n=6), glyburide twice a day (n=7), or chlorpropamide (n=5). Then 12 weeks of followup. 2. Eligibility: Type 2 diabetics, not described. 78% had been on oral hypoglycemics. 3. Maximum dose: glyburide—17.5 mg/day chlorpropamide—700 mg/day	No eligible outcome measures. There appears to be substantial baseline inequality in mean fasting serum glucose levels.	No differences in efficacy.
Hollander 2001 Diabetes Care Novo Nordisk	1. 4-week single-blind run-in period, then multicenter, randomized, double-blind trial of nateglinide 120 mg tid (n=51), glyburide 5 mg then 10 mg qd (n=50) or placebo (n=51) and followed for 8 weeks. 2. Eligibility: Type 2 diabetics treated by diet alone for 4 or more weeks, with mean HbgA1c between 6.8% and 11% and BMI between 20 and 35 kg/m2.	No eligible outcome measures.	Purpose of the study was to compare the effects of nateglinide and glyburide on post-meal glucose and insulin levels. Baseline/final fasting plasma glucose levels were: Placebo 11.4 / 11.6 mmol/L Nateglinide 10.6 / 9.8 mmol/L Glyburide 11.9 / 8.4 mmol/L

Appendix D. Included head-to-head trials

Author Year	Design/ Inclusion	Results	Quality	Exclusion criteria	Adverse Drug Events
Glyburide vs. chlorpropamide					
UKPDS 13: 3 year data 1995 British Medical Journal UKPDS 33: 10 year data 1998 Lancet UKPDS 26: 6 year data 1998 Diabetic Medicine *UKPDS recruited 1977-1991, amended in 1988 to add 8 more centers UKPDS 57: 6 year data reported last 8 centers 2002 Diabetes Care Funded by UKPDS Group	Randomized, Multicenter, Open Newly diagnosed Type 2 DM 3 month diet run-in UKPDS 13: 2520 patients Conventional (FPG goal <270mg/dL) n = 209 If diet failed, randomized to SU, metformin or insulin Intensive (FPG goal <108mg/dL): SU (Chlorpropamide maximum 500mg or Glyburide maximum 20mg), insulin, or metformin; metformin added for failures UKPDS 33: 3041 patients Conventional: Intensive: 1234 SU (Chlorpropamide 619 pts, Glyburide 615 pts) **Amended 1988 adding 8 more centers to a total of 23 centers and adding insulin instead of metformin to SU and new SU (Glipizide,maximum 40mg) 23 centers total n = 3867 (1573 SU)	*UKPDS 13:* Intensive at 3 yrs: Post diet run-in wt 76.6 kg median FPG 8.3, A1C 7.2% 918 assigned intensive SU alone Chlorpropamide n=446 A1C Chlorpropamide 6.8%(-0.4%) Glyburide n=472 A1C Glyburide 6.9%(-0.3%) Eventual combination treatment:Chlorpropamide 9%, Glyburide 13% Average age 52, 52% male 81% Caucasian, 10% Asian, 9% African Average weight 80.4kg Untreated FPG 11.2, A1C 9.1% *UKPDS 33: Both groups at 10 years:* Post diet run-in wt 78 FPG 8.0, A1C 7.08% At 10 years: Intensive n=1234 assigned SU+/-metformin Intensive: A1C 7.0% Conventional: A1C 7.9% p<0.0001 Intensive group A1C Chlorpropamide 6.7%, Glyburide 7.2% (p=0.008) Average age 54, 30% male 81% Caucasian Average weight 76kg, BMI 27.2kg/m2 A1C 7.08%, FPG 8 after 3 month diet *UKPDS 26:* 1305 patients either on Chlorpropamide or Glyburide At 6 yrs 44% needed combination treatment *In 1989 A1C method NL (4.5-6.2), equivalent to ADA (4-6), adjusted for prior methods	GOOD	• Ketonuria > 54mg/dL • Serum creatinine >175 micromol/L • MI in previous year • Current angina or CHF • More than 1 major vascular event • Retinopathy requiring laser treatment • Malignant hypertension • Uncorrected endocrine disorder • Contraindicated insulin • Life limiting or severe illness • Inadequate understanding • Unwilling to participate	At 10 years: • Weight gain: Chlorpropamide +2.6 kg Glyburide +1.7 kg • Chlorpropamide/ Glyburide/Diet Per year hypoglycemia: 0.4%/ 0.6%/ 0.1% Any hypoglycemia: 11%/17.7%/1.2% Major hypoglycemia:1.0%/1.4%/0.7% ITT Any hypoglycemia:16%/21%/10% ITT • Chlorpropamide higher BP and use of HTN medicines • Chlorpropamide less < in retinopathy than Glyburide

DM = Diabetes Mellitus; FPG = Fasting Plasma Glucose; SU = sulfonylurea; BMI = Body Mass Index; BP = Blood Pressure; ITT = Intention to Treat; HTN = hypertension; NS = Not Significant; NR = Not Reported; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; bid = twice a day; WHO = World Health Organization; PPPG = Postprandial Plasma Glucose; ADA = American Diabetic Association; NL = Normal Level; FBG=Fasting Blood Glucose

Appendix D. Included head-to-head trials (continued)

Author Year	Design/ Inclusion	Results	Quality	Exclusion criteria	Adverse Drug Events
Micronized glyburide vs. glyburide					
Carlson 1993 Clinical Therapeutics Upjohn	Randomized, Multicenter Type 2 DM on Gly>1 month n = 206 Continue Gly or change to Gly micronized 3 mg Length: 8 weeks	Completed n = 190 Baseline(prior therapy)/final: A1C 7.7%/7.4%(-0.3%), 7.6%/7.5%(-0.1%) Average age 60 Weight at or above ideal 60% male Women were postmenopausal or sterilized 78% Caucasian 12% African American	FAIR	• Ketoacidosis • Abnormal renal/hepatic function • Contraindications to SU • Systemic corticosteroids or other interacting • Agent affecting glucose tolerance in 4weeks, or investigational agent within 2 weeks	• Weight NS change • Lipid NS change • Withdrawls (Micronized Glyburide/Glyburide): Total 4.3% Hyperglycemic 2.9%/2.8% • *Adverse events (Micronized Glyburide/Glyburide):* Total: 61% each group Hyperglycemic 12.5%/10% Hypoglycemic 0.9% each group
Glipizide vs. glyburide					
Kitabchi 2000 American J Medical Sciences NIH/Roerig	Randomized, Double-blind, Type 2 DM for 4.25 years 110-200% ideal body weight n = 18 (25 patients screened) On-therapy FPG Glipizide 169 mg/dL, Glyburide 142 mg/dL 2 month washout Glyburide 2.5-5mg, by 2.5mg/week Glipizide 5, increased 2.5-5mg every 2 weeks until FPG <140 or 2 PPPG <200 Length: 15 months	All reported A1C Baseline/final: Glipizide 6.7%/5.76%(-1.0%) Glyburide 6.4%/5.13%(-1.3%) Final dose: Glipizide: 11mg Glyburide: 10mg Average age 59.7 50% male Race NR BMI 30 kg/m2	FAIR	• Fasting blood sugar≤140 mg/dL • 2 PPPG ≤200 mg/dL • DBP≥100 for 3 months without a diuretic • DBP>100 for 6 months with a diuretic • DM<6months≥10years • Renal or hepatic dysfunction • Pregnancy	• NS weight change • NS lipid change • NS between hypoglycemic agents

DM = Diabetes Mellitus; FPG = Fasting Plasma Glucose; SU = sulfonylurea; BMI = Body Mass Index; BP = Blood Pressure; ITT = Intention to Treat; HTN = hypertension; NS = Not Significant; NR = Not Reported; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; bid = twice a day; WHO = World Health Organization; PPPG = Postprandial Plasma Glucose; ADA = American Diabetic Association; NL = Normal Level; FBG=Fasting Blood Glucose

Appendix D. Included head-to-head trials (continued)

Author Year	Design/ Inclusion	Results	Quality	Exclusion criteria	Adverse Drug Events
Glimepiride vs. glyburide					
Draeger 1996 Horm.Metab.Res. Hoechst	Randomized, Multicenter, Double-blind Type 2 DM n = 1044 2 week run-in 2 months titration 10 months maintenance 2 week washout Fasting blood sugar 163 mg/dL, A1C 8.1% Identical tabs Schedule: glimepiride 1mg, increase at 1 week to maximum 8mg, glyburide 2.5mg, increase at 1 week to maximum 20mg Decreased if FBG<50-70 to FPG≤150 Length: 12 months	*Patients completed:* Glimepiride 398/524 Glyburide 418/520 Baseline/final: A1C 8.1%/8.4% (+0.3%) each ITT NR, confirmed findings of the per protocol analysis Average age 60.2 64% male 74% Caucasian, 26% other Average weight 26.5 kg/m2 4 years taking an oral hypoglycemic 6 years since DM onset at age 54	FAIR	• Oral hypoglycemic failure • Insulin use in 12 months • Sensitivity • Renal or hepatic dysfunction • Gastrointestinal absorption disorder • Ketonuria with glycosuria • Acute infection • Blood diseases • Pregnancy • Nursing • Drugs that increase glucose	• NS weight changes • NS lipid changes • *Withdrawls (Glimepiride/Glyburide):* Hypoglycemia 11%/14% • Adverse events reported: 17%/19%
Repaglinide vs.micronized glyburide					
Wolffenbuttell 1999 Diabetes Care Novo Nordisk	Asymmetric randomization (2:1), Multicenter, Double-blind n = 425 (Repaglinide 286 patients/Micronized Glyburide 139 patients) WHO defined Type 2 DM on six month diet or oral hypoglycemic (A1C>6.5% on diet [2.8-5.7 NL range] A1C<12% on oral hypoglycemic) Prior therapy A1C 7.1, FBG 10.9 1 week washout Repaglinide .5-4 three times a day Glyburide micronized 1.75-10.5 once or twice a day 6-8 weeks titration 12 months maintenance	Completed n = 320 (211:109) Baseline(washout)/final: A1C Repaglinide7.1%/7.7%(-0.1%) Glyburide 7%/7.5%(-0.2%) 91% were previously on oral hypoglycemic, no dose data Average age 61 64% male Dutch and German Average weight 81.5 kg BMI 28.4kg/m2	FAIR	• Abnormal renal crearinine >2520mg/dL • Abnormal hepatic liver transaminases>2xupper limit of normal • Chronic insulin • Active cardiac diagnosis • SBP>200 and/or DBP>110 • Any other contraindicated diagnosis • Contrainications to SU • Pregnant/intending to become pregnant • Lactating • Systemic corticosteroids	• NS weight changes • NS lipid changes • Withdrawls: Total 25% Hypoglycemic 9% each • Adverse events reported: 14%

DM = Diabetes Mellitus; FPG = Fasting Plasma Glucose; SU = sulfonylurea; BMI = Body Mass Index; BP = Blood Pressure; ITT = Intention to Treat; HTN = hypertension; NS = Not Significant; NR = Not Reported; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; bid = twice a day; WHO = World Health Organization; PPPG = Postprandial Plasma Glucose; ADA = American Diabetic Association; NL = Normal Level; FBG=Fasting Blood Glucose

Appendix D. Included head-to-head trials (continued)

Author Year	Design/ Inclusion	Results	Quality	Exclusion criteria	Adverse Drug Events
Repaglinide vs. glyburide					
Landgraf 1999 Eur J Clin Pharm Novo Nordisk	Randomized, Multicenter, Double-blind 401 patients screened WHO Type 2 DM for 1yr after oral SU for 6 months: n = 195 (94:101) FBG 6.2-12mmol, A1C 6.5%-12%,2.78%-5.7% NL range <12% on oral hypoglycemic 1-2 week washout Repaglinide .5-4 three times a day Glyburide 1.75-10.5 once or twice a day 4 weeks titration 10 weeks maintenance	Completed n = 161 (83:78) Baseline(treatment/washout)(unclear if baseline is before or after treatment)/final: A1C: Repaglinide 7.8/7.5% (-0.3%) Glyburide 8/7.6%(-0.4%) All were previously on oral hypoglycemic 90% ended trial at maximum dose Average age 63 58% male 94% Caucasian Average weight 80kg BMI 27.5kg/m2 SU for 6.5 years FBG 12.5, A1C 7.9%	FAIR	• Abnormal renal • Abnormal hepatic • Chronic insulin • Cardiac diagnosis • Severe DM complications • Unaware of hypoglycemia • Investigational drugs • Systemic corticosteroids • Lipid lowering agents	• NS weight change • NS lipid change except >HDL-C in Repaglinide (20.7 vs.19.98mg/dL) (p=0.005) • Withdrawls: Total 15%(3% for adverse drug events) (Repaglinide 12%, Glyburide 23%) • Adverse drug events: Hyperglycemia: 22 episodes (13:9) Hypoglycemia: 35 episodes (Repaglinide 9.5%, Glyburide 8.9%)
Repaglinide vs. glipizide					
Madsbad 2001 Diabetic Medicine Novo Nordisk	Asymmetric randomization (2:1), Multicenter, multi-nation, Double-blind Screened 320 patients, n = 256 (175:81) 1 week washout 1)Repaglinide 5mg 30 minutes before meals, glipizide 5mg; if FBG>9 start 2)Repaglinide 1mg, glipizide 7.5mg;increase if FBG> 7.8 start 3)Repaglinide 2mg, glipizide 10mg 4)Maximum repaglinide 4/glipizide 10mg+5mg w/dinner Decrease dose if FBG<4.4 Follow-up every 2 wks x 3 titration Visits at 1month, every 3 months, 12 month duration	Patients completed: 240:58 Baseline(prior therapy)/final A1C: Repaglinide 7.3/7.49% (+0.2%) Glipizide 7.2/7.98 (+0.8%), p<0.05 **Low dose glipizide (study maximum 15mg/labeled maximum 40 mg) 50% on study maximum dose (15 mg) at end of study** 88% were on previous oral hypoglycemic Average age 60 62% male Scandanavian Average weight 83kg BMI 28kg/m2 DM for 8 years Type 2 DM A1C 6.5-10%	FAIR	• Serum creatinine ≥140 • Liver diagnosis • Proliferate retinopathy • Systolic blood pressure >200, Diastolic blood pressure>110 • Pregnant • Corticosteroids	• NS weight decrease • NS lipid changes • Severe hypoglycemic n=0 • Adverse drug events: Hypoglycemia 15% repaglinide 19% glyburide, Other total 11% and 11% each agent • Withdrawals due to adverse drug events: 26%

DM = Diabetes Mellitus; FPG = Fasting Plasma Glucose; SU = sulfonylurea; BMI = Body Mass Index; BP = Blood Pressure; ITT = Intention to Treat; HTN = hypertension; NS = Not Significant; NR = Not Reported; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; bid = twice a day; WHO = World Health Organization; PPPG = Postprandial Plasma Glucose; ADA = American Diabetic Association; NL = Normal Level; FBG=Fasting Blood Glucose

Appendix D. Included head-to-head trials (continued)

Author Year	Design/ Inclusion	Results	Quality	Exclusion criteria	Adverse Drug Events
Repaglinide vs glimepiride					
Derosa 2003 Clinical Therapeutics Funder nr	Randomized (1:1), single center, double blind ADA Type 2 DM for ≥ 6 months; unsatisfactory glycemic control (HbA1c > 7.0%) with diet and exercise alone n=132 (65:67) 4-week washout (placebo) Repaglinide 1 mg/day Glimepiride 1 mg/d 8 weeks titration 12 months maintenance	Patients completed: 62:62 Baseline/final HbA1c%: Repaglinide: 8.0/6.8(-1.2) Glimepiride: 7.8/6.7(-1.1) **No previous antidiabetic medication use; no dose data** Average age 55 49% male Italian Average weight 76.7kg BMI 26.2 kg/m2	FAIR	• Smoking • Systolic blood pressure >130 mmHg, diastolic blood pressure > 85 mmHg • Coronary heart disease • Serum creatinine > 1.5 mg/dL	• NS weight decrease • NS lipid changes • Severe hypoglycemic nr • Adverse drug events: Dizziness, nausea, headache in glimepiride group • Withdrawals due to adverse drug events: repaglinide=0; glimepiride=2/67(3%)

DM = Diabetes Mellitus; FPG = Fasting Plasma Glucose; SU = sulfonylurea; BMI = Body Mass Index; BP = Blood Pressure; ITT = Intention to Treat; HTN = hypertension; NS = Not Significant; NR = Not Reported; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; bid = twice a day; WHO = World Health Organization; PPPG = Postprandial Plasma Glucose; ADA = American Diabetic Association; NL = Normal Level; FBG=Fasting Blood Glucose

Appendix E. Table 1. Placebo controlled trials of oral hypoglycemics

Author Year Country	Eligibility criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Key Question 2				
Bech 2003 11 countries in Western/Eastern Europe *Fair quality*	Aged at least 40 years and with Type 2 diabetes	Repaglinide 1-4 mg daily vs placebo x 16 weeks Target FPG≤7.8 mmol/l	nr	WHO WellBeing Questionnaire (WHO-WBQ) WHO Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ) EuroQoL health status measure (EQ-5D) Baseline, 4 weeks and 16 weeks
Key Question 4				
Bautista 2003 7 centers in California *Poor quality*	*Mexican Americans* , aged 35-80, with uncontrolled type 2 diabetes, with an FPG level between 120 mg/dL and 225 mg/dL and an HbA1c value of 8.0% to 10.5%	Glimepiride 1-4 mg daily vs placebo x 14 weeks Target FPG ≤ 120 mg/dL	Allowed per investigator discretion; not specified	Change in HbA1c

Appendix E. Table 1. Placebo controlled trials of oral hypoglycemics (continued)

Author Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Key Question 2				
Bech 2003 11 countries in Western/Eastern Europe *Fair quality*	Mean age=47 57.7% male 98.4% Caucasion	Duration of diagnosed diabetes (mean)=2.8 years HbA1c (%) (mean)=7.7%	nr 408 253 (substudy)	54(21%) withdrawn lost to fu nr 253 analyzed
Key Question 4				
Bautista 2003 7 centers in California *Poor quality*	Mean age=49.1 54.2% male 100% Mexican American	Body weight(kg): 81.1 (glimepiride=83.3; placebo=76.3) Diabetes duration(yrs): 4.7 (glimepiride=4.2; placebo=5.7) HbA1c (%): 10.1	90 screened eligible nr 70 randomized (glimepiride=48; placebo=22)	14(20%) withdrawn [glimepiride=7(15%); placebo=7(38%)] lost to fu nr 60 analyzed

Appendix E. Table 1. Placebo controlled trials of oral hypoglycemics (continued)

Author Year Country	Results	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Key Question 2				
Bech 2003 11 countries in Western/Eastern Europe *Fair quality*	WHO-WBQ: Repaglinide=placebo WHO-DTSQ (mean change in total score): Repaglinide= +8.7; placebo= +1.5; p≤0.01 EQ-5D: Repaglinide=placebo	nr	nr	nr
Key Question 4				
Bautista 2003 7 centers in California *Poor quality*	Change in HbA1c: glimepiride= (-2.3) placebo= (-0.7) p<0.001	Non-biased selection: No Low overall or differential loss to follow-up: Yes Adverse event definition adequate: Yes Adequate description of ascertainment technique: Yes Non-biased ascertainment methods: No Statistical analysis of poetntial confounders: No Adequate duration of follow-up: No Rating: Fair-Poor	Repaglinide vs placebo Overall incidence= 27/48(56.3%) vs 13/22(59.1%) Change in body weight(kg)= +2.3 vs (-2.1); p<0.0001	nr

Appendix E. Table 2. Quality assessment of placebo-controlled trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Key Question 2							
Bech, 2003	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported
Key Question 4							
Bautista, 2003	Method not reported	Method not reported	No	Yes	Not reported	Not reported	Not reported

Appendix E. Table 2. Quality assessment of placebo-controlled trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Maintenance of comparable groups?	Quality Rating	Highly selected population?
Key Question 2						
Bech, 2003	Yes No No No	Not reported Not reported	Yes	Yes	Fair	Pharmacotherapy-naïve patients recruited to substudy from main protocol
Key Question 4						
Bautista, 2003	Yes No Yes No	Yes No	No	Not reported	Poor	Pharmacotherapy-naïve patients

Appendix E. Table 2. Quality assessment of placebo-controlled trials

Author, Year Country	Exclusion criteria for recruitment	Funding	Control group standard of care?	Relevent to key questions?
Key Question 2				
Bech, 2003	Current/recent cardiac disorders or hepatic disease; pregnancy; severe uncontrolled hypertension; systemic corticosteoid treatment; previous treatment with oral antidiabetic agents; abuse of recreational drugs, including alcohol; and recent participation in a clinical drug trial	Not reported	Yes	Yes
Key Question 4				
Bautista, 2003	Pharmacologic therapy for diabetes during previous 3 months or >6 months of continuous/intermittent insulin therapy; clinically relevant medical or psychological condition; history o fdrug or alcohol abuse within 1 year of study entry; participation in an investigational drug study within 1 month of study entry; pregnancy or lactation	Aventis	Yes	Yes