

# Drug Class Review on Oral Hypoglycemics



## Update #3: Preliminary Scan Report #3

May 2009

**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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**OBJECTIVE:**

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

**Date of Last Update:**

Update #2 Final Report was completed in May of 2005.

**Date of Previous Preliminary Update Scans**

Preliminary Update Scan #1: January 2007

Preliminary Update Scan #2: February 2008

**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 (sulfonylureas and short-acting secretagogues) differ in the progression or occurrence of clinically relevant outcomes?

**Key Question 2.** For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in the ability to reduce HbA1C levels?

**Key Question 3.** For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in safety or adverse effects?

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

## **Inclusion Criteria**

### Population

Adult patients with Type 2 diabetes. Subgroups of interest will include, but are not limited to differences by race, age (older adult versus younger adult), gender and patients with chronic stable angina.

### Intervention

- Sulfonylureas: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide (both immediate and extended release formulations included)
- Short-acting secretagogues: repaglinide and nateglinide

### Effectiveness outcomes

- Lowering of HbA1c
- Clinically relevant outcomes:
  - Time to requiring insulin
  - Progression or occurrence of long-term 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)
  - Exercise tolerance
  - Complications of diabetes
  - All-cause mortality
  - Quality of life

### Safety outcomes:

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (e.g., hypoglycemia, weight gain, or effects on lipids)

### Study designs

1. For effectiveness, study is a double-blind, randomized controlled trial in an outpatient setting (including emergency department) or good quality systematic reviews. Crossover trials will be included.
2. For safety, controlled clinical trial, observational study, or drug-drug interaction study.

## METHODS

### Literature Search

To identify relevant citations, we searched MEDLINE (February 2008 to May 2009). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X2).

### Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### Overview

We identified 42 potentially relevant citations. Of those, there are 2 new potentially relevant controlled clinical trials (Appendix A). Table 1 below summarizes the comparisons addressed in each new trial. Both focused on glycemic control and did not report any ‘clinically relevant outcomes’.

**Table 1. New head-to-head trials for Update Scan #3**

Author Year	Comparison
Derosa 2009	Nateglinide vs glibenclamide, both in combination with metformin
Schwartz 2008	Nateglinide vs glyburide, both in combination with metformin

In addition, Table 2 provides a cumulative list of the 11 head-to-head trials identified in the first and second preliminary update scans, none of which reported any ‘clinically relevant outcomes’. Therefore, taken together, now there are a total of 13 head-to-head trials that would likely be added in a full update of this review.

**Table 2. Head-to-head trials identified in previous scans**

Author Year	Comparison
Anwar 2006	Glimepiride vs repaglinide
Cesur 2007	Glimepiride vs repaglinide vs insulin glargine
DeRosa 2007	Nateglinide vs glibenclamide
Go 2004	Glipizide GITS vs glibenclamide
Karadas 2005 (DIACOM)	Glicazide MR vs glibenclamide bid
Li 2007	Nateglinide vs repaglinide
Papa 2006	Repaglinide vs glibenclamide
Ristic 2007	Nateglinide vs gliclazide, both in combination with metformin
Rizzo 2005	Repaglinide vs glimepiride

Rosenstock 2004	Repaglinide vs nateglinide
Sari 2004	Glimepiride vs gliclazide vs repaglinide

**New Drugs**

None

**New Indications**

None

**New Safety Alerts**

None

## APPENDIX A

Derosa, G., A. D'Angelo, et al. (2009). "Nateglinide and glibenclamide metabolic effects in naive type 2 diabetic patients treated with metformin." Journal of Clinical Pharmacy & Therapeutics **34**(1): 13-23.

**BACKGROUND AND OBJECTIVE:** Most antidiabetic agents target only one of several underlying causes of diabetes. The complementary actions of the glinides and the biguanides may give optimal glycemic control in patients with type 2 diabetes mellitus. The aim of the present study was to compare the effects of nateglinide plus metformin with glibenclamide plus metformin on glucose and lipid metabolism, and haemodynamic parameters in patients with type 2 diabetes mellitus. **METHODS:** We enrolled 248 type 2 diabetic patients. Patients were randomly assigned to receive nateglinide (n = 124) or glibenclamide (n = 124), after 6 months of run-in, in which we titrated nateglinide (starting dose 180 mg/day), glibenclamide (starting dose 7.5 mg/day), and metformin (starting dose 1500 mg/day). The final doses were (mean +/- standard deviation), 300 +/- 60, 12.5 +/- 2.5, and 2500 +/- 500 mg/day, respectively. We followed these patients for 1 year after titration. We assessed body mass index (BMI), fasting (FPG) and post-prandial (PPG) plasma glucose, glycosylated haemoglobin (HbA(1c)), fasting (FPI) and post-prandial (PPI) plasma insulin, homeostasis model assessment (HOMA) index, and lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B)], systolic blood pressure (SBP), and diastolic blood pressure (DBP). All variables were evaluated at baseline and after 3 and 6 months in the run-in period, and at baseline, and after 3, 6, 9 and 12 months for both treatment groups. **RESULTS AND DISCUSSION:** Body mass index did not show any significant change during the study. We observed a significant improvement from baseline to 1 year on HbA(1c) (P < 0.01 vs. baseline and vs. glibenclamide group, respectively), FPG (P < 0.01 vs. baseline), PPG (P < 0.01 vs. baseline), and on HOMA index (P < 0.05 vs. baseline) in the nateglinide group. In the glibenclamide group, we found significant changes in HbA(1c) (P < 0.05 vs. baseline), FPG (P < 0.01 vs. baseline), PPG (P < 0.05 vs. baseline), and HOMA index (P < 0.05 vs. baseline). No significant change was observed in TC, LDL-C, HDL-C, Tg, Apo A-I, Apo B, SBP, DBP and HR in either group after 3, 6, 9 and 12 months. These effects of nateglinide and glibenclamide on insulin-resistance parameters are in agreement with previous reports. Contrarily to previous reports, we did not observe any significant BP change in patients treated with glibenclamide. Although both nateglinide and glibenclamide attenuated PPG and HOMA index, they did not have significant effects on lipid metabolism, as already shown in subjects with type 2 diabetes and good glycemic control. **CONCLUSION:** Nateglinide improved glycemic control better than glibenclamide in combination with metformin.

Schwarz, S. L., J. E. Gerich, et al. (2008). "Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naive elderly patients with type 2 diabetes." Diabetes, Obesity & Metabolism **10**(8): 652-60.

**AIM:** The aim of this work was to assess the efficacy and tolerability of nateglinide alone or in combination with metformin in elderly patients with type 2 diabetes (T2DM). **METHODS:** Study 1 was a 12-week, multicentre, randomized, double blind and placebo-controlled study of nateglinide monotherapy (120 mg, before meals) in 66 drug-naive

patients with T2DM aged  $\geq 65$  years. Study 2 was a 104-week, multicentre, randomized, double blind and active-controlled study of nateglinide (120 mg, before meals) or glyburide (up to 5 mg bid) in combination with metformin (up to 1000 mg bid) in 69 treatment-naive patients with T2DM aged  $\geq 65$  years. HbA(1c), fasting and postprandial glucose levels, and safety assessments were made. RESULTS: In Study 1, nateglinide significantly reduced HbA(1c) from baseline (7.6  $\pm$  0.1% to 6.9  $\pm$  0.1%; Delta = -0.7  $\pm$  0.1%,  $p < 0.001$ ) and compared with placebo (between-group difference = -0.5%,  $p = 0.004$  vs. nateglinide). No hypoglycaemia was reported. In Study 2, combination therapy with nateglinide/metformin significantly reduced HbA(1c) from baseline (7.8  $\pm$  0.2% to 6.6  $\pm$  0.1%; Delta = -1.2  $\pm$  0.2%,  $p < 0.001$ ), as did glyburide/metformin (7.7  $\pm$  0.1% to 6.5  $\pm$  0.1%; Delta = -1.2  $\pm$  0.1%,  $p < 0.001$ ). There was no difference between treatments ( $p = 0.310$ ). One nateglinide/metformin-treated patient experienced a mild hypoglycaemic episode compared with eight episodes in eight patients on glyburide/metformin; one severe episode led to discontinuation. Target HbA(1c) ( $< 7.0\%$ ) was achieved by 60% of patients receiving nateglinide (Study 1) and 70% of nateglinide/metformin-treated patients (Study 2). CONCLUSION: Initial drug treatment with nateglinide, alone or in combination with metformin, is well tolerated and produces clinically meaningful improvements in glycaemic control in elderly patients with T2DM.