Treatment of Patients Over 64 Years of Age With Type 2 Diabetes

Experience from nateglinide pooled database retrospective analysis

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OBJECTIVE — To evaluate the impact of renal impairment (RI) (estimated creatinine clearance [Cl_{cr}] <60 ml/min per 1.73 m^2) and low baseline HbA_{1c} (<7.5%) on comorbidity in patients with type 2 diabetes, and to assess the efficacy and safety of nateglinide monotherapy in these patients and in subgroups of patients over age 64 years (elderly) and elderly with RI.

RESEARCH DESIGN AND METHODS — Retrospective subgroup analyses were performed on pooled data from all completed nateglinide studies (12 randomized, double blind trials and 1 open trial) in patients with type 2 diabetes. A total of 3,702 patients with ≥1 postbaseline safety evaluation received monotherapy with nateglinide (n = 2,204), metformin (n = 436), glyburide (n = 293), or placebo (n = 769). Efficacy (HbA_{1c}) was evaluated in pooled data from four studies with similar design using 120 mg nateglinide (n = 544) versus placebo (n = 521). Evaluations were performed in the overall population and subgroups of patients over age 64 years. Specific considerations were given to RI, comorbidity, and baseline HbA_{1c}.

RESULTS — Patients over age 64 years (n = 1,170) represented 31.6% of the study population. Undiagnosed RI was common in the elderly with 83.4% of all patients being in this subgroup. Patients over 64 years with RI had a higher prevalence of cardio- and microvascular comorbidity compared with the overall population and all patients over age 64 years. Statistically significant HbA_{1c} reductions versus placebo were observed with nateglinide in patients over age 64 years and elderly with RI patients at study end point (−0.9% and −1.1% in each subgroup, $P < 0.01$). Nateglinide was well tolerated with a low incidence of hypoglycemia in all subgroups, including those with RI and low baseline HbA_{1c}.

CONCLUSIONS — RI and comorbidity are common in patients over age 64 years with type 2 diabetes. Nateglinide was effective and well tolerated in all treated patients. In subgroups in which metformin and long-acting sulfonylureas must be used with caution, nateglinide had a low risk of adverse events and hypoglycemia.

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The highest prevalence of type 2 diabetes in the U.S. is observed in the elderly population, with a projected prevalence of 13.6% in men and 14.7% in women aged 65–74 years (1). The therapeutic principles of managing type 2 diabetes in the elderly are no different from those in younger patients, but the strategies need to be cautiously individualized. Comorbid conditions are common in the elderly with type 2 diabetes and frequently influence the choice and intensity of treatment. Treatment to target with current antihyperglycemic agents is often not attempted because of the risk of severe hypoglycemia and possible exacerbation of cognitive deficiencies or coexisting cardiovascular conditions (2–6).

Most oral blood glucose-lowering agents must be used with caution in patients with renal impairment (RI) or in the presence of comorbidity. RI has long been recognized to be common in the elderly, but its prevalence has not been fully appreciated. Decreased creatinine clearance (Cl_{cr} <60 ml/min per 1.73 m^2) was observed in 77% of the U.S. elderly population with type 2 diabetes, whereas serum creatinine levels were increased in only 43% (7). Metformin should be used with caution in case of limited renal function because RI increases the risk of lactic acidosis (8–10). Treatment with sulfonylureas (SUs) have a 36% higher annual risk of documented hypoglycemia in older than in younger patients (11). In a review of drug-induced hypoglycemic coma in type 2 diabetes, 82.3% of patients were aged ≥60 years and ≥65% had Cl_{cr} <80 ml/min (12). Nateglinide is a novel oral glucose-lowering agent with a rapid onset of action and a short pharmacokinetic and pharmacodynamic half-life (13,14). Nateglinide induces a more physiological insulin secretion and prandial plasma glucose response than SUs, is effective in reducing HbA_{1c} through prandial plasma glucose, and has a low incidence of hypoglycemic events (15,16). Nateglinide is rapidly and extensively metabolized, and no dosage adjustment is required in patients with mild to severe renal or mild hepatic insufficiency (17), which are clinical conditions often observed in the elderly.

The purpose of this analysis was to evaluate the impact of age, RI (estimated Cl_{cr} <60 ml/min per 1.73 m^2), and low baseline (BL) HbA_{1c} (<7.5%) on comorbidity in patients with type 2 diabetes and

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Abbreviations: AE, adverse event; BL, baseline; Cl_{cr}, creatinine clearance; FPG, fasting plasma glucose; ITT, intent-to-treat; RI, renal impairment; SAE, serious adverse event; SU, sulfonylurea.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

to assess the efficacy and safety of nateglinide monotherapy in all patients and in subgroups of patients over age 64 years and patients over age 64 years with RI after pooling all completed nateglinide studies.

RESEARCH DESIGN AND METHODS

— Data from all nateglinide phase II and III trials completed by February 2001 were pooled with the objective of establishing the safety and efficacy of nateglinide monotherapy in the overall population and in subgroups of interest, such as the elderly (aged >64 years). Specific considerations were given to RI, comorbidity, and BL HbA_{1c}. A total of 13 trials were pooled, six of which are published (16,18–22). Twelve were randomized, double blind, placebo, and/or active-controlled trials of similar design; one small trial in patients with RI was open label (n = 34). Data were pooled according to monotherapy treatment received.

Patient populations

The majority (81.3%) of the nateglinide monotherapy patients (n = 2,204) had no prior blood glucose-lowering therapy other than diet and exercise or had discontinued therapy ≥8 weeks before randomization. In the remaining 19.7% nateglinide patients, patients were on previous blood glucose-lowering therapy for ≥3 months before randomization and were switched to nateglinide during the double-blind period. Therefore, nateglinide was initiated at the time of randomization in all studies, whereas metformin and glyburide were continued unchanged in most studies and initiated at the time of randomization in only two studies.

Nateglinide (fixed doses of 30, 60, 120, or 180 mg) was administered three times daily before meals (a.c.). Either 500 mg of metformin thrice or 1 g twice daily and 10 mg of glyburide were administered following package insert guidelines.

Key inclusion criteria for most trials included: diagnosis with type 2 diabetes ≥3 months before study, age ≥30 years, BMI 20–35 kg/m^2, and HbA_{1c} 6.8–11%. General study exclusion criteria included: significant metabolic or vascular complications of diabetes, insulin-dependent diabetes, and conditions with the potential to affect the clinical stability of diabetes. Patients with significant hepatic (≥2 times upper limit of normal), biliary, or renal function abnormalities were also excluded. Exclusion limits for serum creatinine ranged from ≥160 μmol/l to ≥220 μmol/l except in studies that used metformin in which lower limits were used (≥133 μmol/l for men and ≥124 μmol/l for women).

Safety evaluation

All monotherapy patients (30–180 mg nateglinide a.c., 10 mg glyburide, 1.5–2 g metformin daily, or placebo) who had ≥1 post-BL safety evaluation were entered in the pooled safety analysis.

Safety variables included adverse events (AEs), serious AEs (SAEs), medical history, and evaluation of hypoglycemia. Hypoglycemic events were considered as confirmed if plasma glucose levels were ≤3.3 mmol/l. All patients were supplied with a glucose-monitoring device (One Touch II, Lifescan) for self–blood glucose monitoring. Patients recorded hypoglycemic episodes in a diary. Cl_{cr} was estimated by using the Cockcroft-Gault formula corrected for body surface area: Cl_{cr} (ml/min) = (140 − age [years] × body weight [kg] and K/serum creatinine [μmol/l] with K = 1.23 for men and 1.05 for women) per 1.73 m^2 (23,24–26). RI was defined as a Cl_{cr} <60 ml/min per 1.73 m^2. All laboratory values, including serum creatinine, were measured in a central laboratory.

The prevalence of micro- and macrovascular complications were derived from data on the history of diabetes and possibly related medical conditions recorded in 10 of the 13 studies, representing roughly 75% of all patients. The predefined macrovascular conditions (angina pectoris, myocardial infarction, stroke, hypertension, etc.) and microvascular conditions (retinopathy, nephropathy, neuropathy, and foot ulcer) were reported at study entry.

Efficacy evaluation

HbA_{1c} was evaluated after pooling four randomized, double-blind studies with similar design and patient population using 120 mg nateglinide a.c. and placebo patients (pooled intent-to-treat [ITT] population). Three of these studies are published (16,18,22). Comparative efficacy analyses with metformin and glyburide were not performed, as most patients on comparative treatments had achieved maximal reductions in HbA_{1c} before study randomization.

Statistical methodology

The pooled ITT population was used for efficacy evaluation of the changes from BL in HbA_{1c} at end point (90% of patients had an HbA_{1c} value between week 12 and week 24 postrandomization). The last observation carried forward approach was used for patients who had no HbA_{1c} assessment at the scheduled final visit. To compare the treatment effect of 120 mg nateglinide with placebo, an ANCOVA that included fixed effect for study, treatment, center (nested in study), BL HbA_{1c} value, and treatment by BL interaction was used. The model was checked by examining the residual plots, and these revealed no obvious trend (the consistency of treatment effect across studies was examined by including treatment by study interaction into the above ANCOVA model and was found not to be significant ($P > 0.1$). Using end point HbA_{1c} as the independent variable, the same ANCOVA model was fitted, and identical results regarding treatment interference were obtained.

For safety evaluation, a Fisher's exact test was used for comparing the incidences between the subpopulations or between the treatment groups. All tests were two sided with significance level of 0.05.

Safety and efficacy analyses were performed in the overall population, patients over age 64 years, and patients over age 64 years with RI (calculated Cl_{cr} <60 ml/min per 1.73 m^2).

RESULTS

— A total of 3,702 patients with more than one post-BL safety evaluation received monotherapy with either nateglinide (n = 2,204), metformin (n = 436), glyburide (n = 293), or placebo (n = 769) for ≤6 months of treatment duration.

Most patients on glyburide and metformin therapy were on a stable dose at randomization. In these patients, HbA_{1c} remained unchanged or increased slightly during the course of the study.

Demographic and clinical characteristics

BL demographic and clinical data of patients in the pooled safety population were similar across treatment groups. Patients were predominantly male with a mean age of ~60 years and had poorly controlled HbA_{1c} at BL (Table 1). Patients receiving nateglinide and placebo had less

Table 1—*Demographic and clinical characteristics of patients in the safety analyzable population (pooled data from 13 studies,* N = *3,702)*

Clinical feature	Nateglinide	Metformin	Glyburide	Placebo
All patients				
n	2,204	436	293	769
Age (years)†	59.2 ± 10.6	57.1 ± 10.3	59.5 ± 10.3	58.5 ± 10.8
Duration diabetes (years)*	5.1 ± 5.7	5.6 ± 5.8	6.7 ± 5.6	4.2 ± 4.6
BMI (kg/m^2)*	29.1 ± 3.8	29.5 ± 4.0	28.8 ± 3.8	29.4 ± 3.7
HbA_{1c} (%)*	7.8 ± 1.2	8.3 ± 1.1	8.1 ± 1.0	7.8 ± 1.2
FPG (mmol/l)*	9.6 ± 2.4	10.5 ± 2.4	10.5 ± 2.8	9.9 ± 2.5
Serum creatinine (μmol/l)*	91.5 ± 18.3	90.5 ± 14.7	87.7 ± 15.7	90.1 ± 17.1
Cl_{cr} (ml/min per 1.73m^2)*	77.1 ± 20.0	80.1 ± 18.6	79.3 ± 21.7	79.1 ± 20.6
Cardiovascular condition (%)	47.5	49.5	43.3	48.1
Microvascular condition (%)	59.2	61.0	57.7	60.5
Patients >64 years				
n	737	104	92	237
Age (years)*	70.6 ± 4.5	70.4 ± 4.0	71.4 ± 4.4	70.6 ± 4.3
Duration diabetes (years)*	6.5 ± 7.0	7.5 ± 7.3	8.7 ± 6.9	5.3 ± 5.4
BMI (kg/m^2)*	28.4 ± 3.7	28.1 ± 4.0	27.7 ± 3.8	28.4 ± 3.8
HbA_{1c} (%)*	7.6 ± 1.0	8.2 ± 1.0	7.9 ± 1.0	7.7 ± 1.1
FPG (mmol/l)*	9.2 ± 2.1	10.0 ± 2.1	10.0 ± 2.9	9.5 ± 2.2
Serum creatinine (μmol/l)*	96.4 ± 19.6	96.0 ± 15.2	91.3 ± 15.6	94.1 ± 16.8
Cl_{cr} (ml/min per 1.73m^2)*	61.5 ± 12.4	61.1 ± 10.7	63.3 ± 14.9	62.8 ± 12.9
No. (%) age ≥70 years	387 ± 52.5	53 ± 51.0	58 ± 63.0	119 ± 50.2
Cardiovasclar condition (%)	59.2	58.7	52.2	57.7
Microvascular condition (%)	70.4	72.8	67.4	69.2
Patients >64 years with RI†				
n	333	51	88	100
Age (years)*	72.9 ± 4.9	72.2 ± 4.4	74.2 ± 4.1	72.9 ± 4.7
Duration diabetes (years)*	7.1 ± 8.2	8.5 ± 6.5	8.6 ± 7.0	6.0 ± 6.0
BMI (kg/m^2)*	27.2 ± 3.5	26.6 ± 3.3	26.8 ± 3.7	26.6 ± 3.6
HbA_{1c} (%)*	7.5 ± 1.0	8.1 ± 1.0	7.8 ± 1.0	7.5 ± 1.1
FPG (mmol/l)*	8.9 ± 2.1	9.7 ± 2.1	9.4 ± 3.0	9.1 ± 2.0
Serum creatinine (μmol/l)*	108.0 ± 20.4	104.1 ± 13.7	101.5 ± 14.4	105.3 ± 16.3
Cl_{cr} (ml/min per 1.73m^2)*	50.9 ± 7.1	52.2 ± 5.4	50.6 ± 7.2	51.1 ± 6.4
No. (%) age ≥70 years	244 ± 73.3	34 ± 66.7	33 ± 86.8	69 ± 69.0
Cardiovascular condition (%)	64.9	54.5	71.1	60.3
Microvascular condition (%)	74.3	68.2	76.3	75.0

*Data are means ± SD. †RI: calculated Cl_{cr} <60 ml/min per 1.73m^2.

advanced disease than the patients who were treated with metformin or glyburide, as indicated by the lower HbA_{1c} values and shorter times from diagnosis. Hypertension was the most frequent macrovascular and neuropathy the most frequent microvascular condition in all subgroups (Table 1).

Approximately one-third of patients (31.6% overall) were persons over age 64 years with a mean age of ~70 years. In comparison with the overall population, persons over age 64 years had a longer duration of diabetes and lower BMI, HbA_{1c}, and fasting plasma glucose (FPG) at BL. Mean serum creatinine values in elderly were within the normal range, but their mean estimated Cl_{cr} (mean 61.1–63.3 ml/min) was just above the value defined as RI. Persons over age 64 years had a higher incidence of micro- and macrovascular complications than the overall population (Table 1). Persons over age 64 years had an increased prevalence of neuropathy (present in ~20% of all groups), hypertension (present in 48–53%), myocardial infarction (present in 6.5–8.7%), and stroke (present in 4.3–6.5%).

Almost one-half of the persons over age 64 years had RI (nateglinide, 333 of 737, 45.2%) even though their mean serum creatinine values were within the normal range. Most persons with RI (nateglinide, 333 of 398, 83.7%) were over age 64 years. Aging was the greatest determinant of RI, the proportion of patients ≥70 years being higher in the elderly with RI than the elderly group (nateglinide, 73.3% vs. 52.5%). A trend toward lower mean BMI, HbA_{1c}, and FPG was observed in elderly with RI compared with elderly patients. A vast majority of elderly patients with RI had microvascular (68.2–76.3%) and macrovascular (54.5–71.1%) complications (Table 1). Angina pectoris, myocardial infarction, and stroke were the major macrovascular complications in all populations with prevalences of 11.0, 7.0, and 4.6%, respectively, in patients over age 64 years.

Efficacy

In the overall population, mean ± SD BL HbA_{1c} values were 8.3 ± 1.1% in the 120 mg nateglinide group (n = 544) and 8.2 ± 1.1% in the placebo group (n = 521). In the elderly and elderly with RI subgroups, mean HbA_{1c} values were lower than in the respective overall populations (Table 2).

At study end point, the difference versus placebo (SE) in adjusted mean change from BL in HbA_{1c} was −0.8% (P < 0.001) in all patients on 120 mg nateglinide a.c. In elderly and elderly with RI, the decrease was −0.9% (P < 0.001) and −1.1% (P = 0.002). In elderly patients on nateglinide (n = 107) with a low HbA_{1c} at BL (HbA_{1c} <7.5%, mean 7.1%), a mean decrease in HbA_{1c} of −0.7% was observed.

Tolerability

Overall, all active treatments were well tolerated in all groups with few differences from placebo.

Nateglinide tolerability was similar to that of placebo in all subgroups with age or renal function having little impact on the incidence of AEs, SAEs, and AE discontinuations.

Glyburide was well tolerated in the overall population but showed a significantly higher incidence of discontinuations and SAEs in patients over age 64 years with RI (discontinuation, 10.5%; SAEs, 15.8%) compared with all glyburide patients (discontinuation, 3.8%; SAEs, 5.8%; both P < 0.05) (Table 3). The relatively high dose of glyburide (10 mg daily) may not have been optimal in patients over age 64 years.

On metformin, discontinuations were higher in patients over age 64 years

Table 2—*Change from baseline in HbA_{1c} (%) at end point in all patients, patients >64 years, and in patients >64 years with RI* (pooled ITT population from four placebo-controlled studies)*

Patient population and treatment group	*n*	BL	Change from baseline		Difference from placebo†	Difference from placebo (*P* value†)
			Mean ± SE	Adjusted mean ± SE		
All patients						
Placebo	521	8.19 ± 0.05	0.32 ± 0.05	0.31 ± 0.05‡		
Nateglinide 120 mg	544	8.27 ± 0.05	−0.47 ± 0.05	−0.48 ± 0.05†	−0.78 ± 0.07	<0.001
Patients >64 years						
Placebo	164	8.06 ± 0.08	0.26 ± 0.08	0.18 ± 0.09‡		
Nateglinide 120 mg	163	8.19 ± 0.08	−0.64 ± 0.07	−0.72 ± 0.10‡	−0.90 ± 0.13	<0.001
Patients >64 years with RI*						
Placebo	63	7.99 ± 0.12	0.25 ± 0.14	0.41 ± 0.23		
Nateglinide 120 mg	60	8.04 ± 0.12	−0.65 ± 0.11	−0.73 ± 0.23‡	−1.14 ± 0.34	0.002

Data are means ± SE unless otherwise indicated. RI: calculated creatinine clearance <60 ml/min per 1.73 m^2. †Results were from an ANCOVA model containing study, treatment, investigative site (nested in study), baseline value, and treatment by baseline. ‡Statistically significantly change from baseline ($P < 0.05$).

and in patients over 64 years with RI (9.6% and 11.8%, respectively) compared with 6.9% in the overall population due to gastrointestinal AEs. Diarrhea was more common with metformin in the elderly than in the overall population (16.3% vs. 12.4%).

Hypoglycemia

Confirmed hypoglycemia was observed in 2.2% and 3.0% of elderly subgroups compared with 2.2% incidence in the overall population for patients on nateglinide. Hypoglycemic events led to discontinuation of nateglinide in 0.5% of the elderly and 0.6% of patients overall (data not shown).

Events suggestive of hypoglycemia were observed in all treated groups including placebo but had the highest incidence on glyburide in all subgroups (Table 3).

The only AE more common on nateglinide than on placebo was hypoglycemia. The incidence of events suggestive of hypoglycemia on nateglinide were similar in patients over age 64 years and elderly with RI subgroups compared with the overall population (9.9% and 10. 2% vs. 11.1%, Table 3).

The incidence of hypoglycemia was influenced by BL HbA_{1c} in active treated groups. The increase in incidence of confirmed hypoglycemia in patients with a BL HbA_{1c} <7.5% was, however, limited in all nateglinide subgroups (3.9% in the 181 elderly with RI and low HbA_{1c} vs. 3% in the total 333 elderly with RI).

CONCLUSIONS — Limited data on treatment of type 2 diabetes in older patients are available, although patients over age 64 years represent one-half of the diabetes population (1,2,5,27). Comorbidity is frequent among elderly patients, but little is known about its impact on drug tolerability. The increased risk of hypoglycemia in the elderly treated with SUs is well documented (11,12).

The impact of reduced renal function on efficacy and tolerability of antidiabetic treatments is difficult to assess because renal function is not easy to measure, and serum creatinine levels do not adequately reflect renal function in the elderly. The calculated Cl_{cr} used in this analysis is an accepted method to assess renal function in the general population and in the elderly (23,26). Calculating Cl_{cr} using either the Cockroft-Gault formula or similar nomograms helps to identify patients at risk of AEs when receiving renally eliminated drugs. Age is recognized as a key determinant in decreased glomerular filtration rate. The results presented confirm that patients with normal serum creatinine values who have reduced calculated Cl_{cr} have a higher prevalence of cardiovascular and microvascular conditions.

The data presented are not devoid of the problems associated with retrospective analyses. However, the fact that all data from all analyzable patients completed at a given time point are presented limits this criticism.

Undiagnosed decreased renal function was present in nearly 50% of the elderly population. The prevalence of RI was lower in this analysis than that reported in U.S. elderly (7), probably due to the exclusion limits for serum creatinine.

Nateglinide therapy was shown to be effective in elderly and elderly with RI patients as compared with placebo. The efficacy was similar to or slightly better than that observed in the overall population of the separate studies (16,18,22). It is known that glucose values increase with age, with prandial (postload) glucose levels increasing more than fasting levels (~0.83 vs. 0.06–0.11 mmol/l per decade) (23,26). Therefore, a treatment addressing prandial more than fasting glucose levels may be more appropriate in newly diagnosed elderly not responding to diet and exercise. However, this database does not allow efficacy comparisons versus glyburide because most patients on glyburide were already on SUs at least 3 months before randomization. The current analysis underscores the need for prospective trials in these patient populations.

Nateglinide was well tolerated in all patients, including patients over age 64 years with no difference in any tolerability parameter (percentage of AEs, discontinuations for AEs, and SAEs) from the overall population, including events of hypoglycemia and confirmed hypoglycemia. Hypoglycemia was the only nateglinide-related AE, which was confirmed in 2.2% of elderly and all patients and 3.0% of elderly patients with RI.

Overall, metformin was well tolerated in the total patient population. Elderly patients on metformin had a higher incidence of AEs and discontinuations than the overall metformin population. This may be related to the accumulation of metformin in the presence of RI (6,8,23).

Glyburide was well tolerated in the overall population but showed an in-

Table 3—*Incidence of adverse events in the safety analyzable population (pooled data from 13 studies* (n = *3,702*)

	Nateglinide	Metformin	Glyburide	Placebo
All patients				
n	2,204	436	293	769
Percentage with ≥1 AE	60.7	69.0	59.4	61.4
Percentage with discontinuation for AEs	4.7	6.9	3.8	4.3
Percentage with SAEs (death)	3.4 (0.2)	3.0 (0.2)	5.8 (1.0)	4.6 (0)
Events of hypoglycemia	11.1	7.1	19.1	4.4
Baseline HbA_{1c} <7.5%	15.3	11.6	32.3	6.3
Confirmed hypoglycemia*	2.2	0.7	6.8	0.9
Baseline HbA_{1c} <7.5%	3.8	0.8	12.5	1.7
Gastrointestinal AEs				
Diarrhea	2.8	12.4	2.0	3.0
Nausea	2.6	5.3	2.0	3.8
Dyspepsia	1.7	4.4	1.4	2.2
Patients >64 years				
n	737	104	92	237
Percentage with ≥1 AE	62.6	76.9	55.4	64.1
Percentage with discontinuation for AEs	5.0	9.6	6.5	5.9
Percentage with SAEs (death)	5.7 (0.3)	2.9 (0)	8.7 (3.3)	6.8 (0)
Events of hypoglycemia	9.9	9.6	19.6	5.9
Baseline HbA_{1c} <7.5%	11.5	7.7	36.4	5.8
Confirmed hypoglycemia*	2.2	0	6.5	0.4
Baseline HbA_{1c} <7.5%	3.2	0	12.1	0.8
Gastrointestinal AEs				
Diarrhea	3.8	16.3	1.1	3.4
Nausea	2.7	5.8	2.2	2.1
Dyspepsia	2.3	10.6	0	3.8
Patients >64 years with RI†				
n	333	51	38	100
Percentage with ≥1 AE	65.2	66.7	60.5	64.0
Percentage with discontinuation for AEs	6.3	11.8	10.5	6.0
Percentage with serious AEs (death)	6.6 (0)	0 (0)	15.8 (5.3)	6.0 (0)
Events of hypoglycemia	10.2	9.8	15.8	6.0
Baseline HbA_{1c} <7.5%	11.0	6.7	42.9	3.6
Confirmed hypoglycemia*	3.0	0	7.9	0
Baseline HbA_{1c} <7.5%	3.9	0	21.4	0
Gastrointestinal AEs				
Diarrhea	5.4	13.7	2.6	1.0
Nausea	2.7	9.8	2.6	2.1
Dyspepsia	3.0	11.8	0	3.0

*Confirmed hypoglycemia: plasma glucose level ≤3.3 mmol/l. †RI: calculated creatinine clearance <60 ml/min per 1.73m^2.

creased incidence of AEs, discontinuation for AEs, and SAEs in patients over age 64 years. Age and renal function had a significant impact on the tolerability of glyburide. This was mainly related to an increased incidence of hypoglycemia. However, this observation should be interpreted with caution because of the relatively small number of patients exposed to glyburide in this subgroup and the use of a fixed 10-mg dose of glyburide. In addition, glyburide appears to have the highest risk of hypoglycemia among SUs, although shorter-acting SUs are not devoid of such a risk (11,12). In contrast, the fact that most patients in the glyburide group were on chronic glyburide therapy at randomization may have underestimated the true risk of hypoglycemia observed with glyburide.

In summary, this retrospective analysis revealed the frequent occurrence of comorbidity and undiagnosed RI among elderly patients with type 2 diabetes and normal serum creatinine values. Nateglinide was effective and well tolerated in all treated patients. In subgroups in which metformin and long-acting SUs must be used with caution, nateglinide had a low risk of AEs and hypoglycemia, including patients with undiagnosed limited renal function.

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