The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus

Rodolfo Guardado-Mendoza[1], Annamaria Prioletta[2], Lilia M. Jiménez-Ceja[1], Aravind Sosale[3], Franco Folli[4]

[1]Department of Medicine and Nutrition, Division of Health Sciences, University of Guanajuato, México
[2]Diabetes Center, ACISMOM Associazione Cavalieri Italiani Sovrano Militare Ordine Di Malta, Italy
[3]Diacon Hospital, Bangalore, India
[4]Department of Medicine, Diabetes Division, University of Texas Health Science Center at San Antonio, Texas, USA

Submitted: 13 November 2012
Accepted: 31 January 2013

Arch Med Sci 2013; 9, 5: 936–943
DOI: 10.5114/aoms.2013.34991

Corresponding author:
Franco Folli MD, PhD
University of Texas Health Science Center
Department of Medicine
Diabetes Division
Mail Stop 7886–7703
Floyd Curl Drive-San Antonio
TX 78229-3900, USA
Phone: 210-567-4826.
E-mail: folli@uthscsa.edu

Abstract

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide, presenting a great challenge to the public health systems due to high morbidity and mortality, because of frequent micro-/macro-vascular complications. Many treatment options are now available, with different efficacy as well as mechanisms of action to improve deranged glucose metabolism. We review some of the available data on derivatives of meglitinide, namely nateglinide and repaglinide. These two compounds increase insulin secretion by a mechanism similar to the one of sulfonylureas, but with a shorter half-life. Nateglinide and repaglinide, derivatives of meglitinides, have characteristic pharmacodynamic and pharmacokinetic properties that, together with their proposed mechanism of action, make them useful for type 2 diabetes mellitus, especially when used in combination therapy.

Key words: meglitinide, repaglinide, nateglinide, glycemic control, post-prandial glucose excursion, hypoglycemia.

Data sources

We performed a systematic Medline search (from September 2012 to December 1994), using the following search terms:
- "meglitinide analogues" and/or "nateglinide" or "repaglinide",
- "repaglinide and sulfonylureas",
- "nateglinide and sulfonylureas".

Eighty-two papers considered relevant for the aim of this review were selected by the authors. When previous systematic reviews were incorporated, we independently examined the individual studies to confirm or extend previous reviews' findings.

Chemical and pharmacodynamic properties

The meglitinide analogues are insulinotropic agents, introduced in 1995 and approved for clinical use in adults with type 2 diabetes mellitus (T2DM) in 2000. They are secretagogue molecules with a more rapid anti-hyperglycemic action and a shorter duration than sulfonylureas, thus providing

better control of post-prandial hyperglycemia and reducing the risk of late hypoglycemia [1, 2].

Repaglinide

Repaglinide was the first meglitinide analogue approved for clinical use in adults with T2DM. Repaglinide is the S(+) enantiomer of 2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid with a molecular weight of 452.6 Da.

The mechanism of action is similar to sulfonylureas, but repaglinide exhibits distinct pharmacological properties in structure, binding profile, duration of action and mechanisms of excretion [3].

Like the sulfonylureas, the insulinotropic action of repaglinide is mediated via adenosine triphosphate (ATP)-dependent potassium channels. Repaglinide stimulates insulin secretion by blocking ATP-dependent potassium channels (KATP) of the pancreatic β-cell, where inhibition of KATP channels results in membrane depolarization and calcium influx through voltage-gated calcium channels. These events lead to an increase in intracellular calcium and subsequent exocytosis of insulin-containing granules.

The KATP channel is a hetero-octameric complex of two different types of protein subunits: an inwardly rectifying K+ channel (KIR) subunit 6.x and a sulfonylurea receptor (SUR). More than one isoform exists for both Kir6.x (Kir6.1, Kir6.2) and SUR (SUR1, SUR2A, SUR2B). Distinct isoforms and splice variants of the SUR subunit are expressed in different tissues and confer many of the pharmacological properties to the KATP channel hetero-octamer. The subunits that are predominantly expressed in pancreatic β-cells are Kir6.2 and SUR1 [4].

Repaglinide binds to the sulfonylurea receptor SUR1 and it seems to have also a separate distinct binding site on β cells, as demonstrated in mouse β cells co-incubated with PPP (3-(3 hydroxyphenyl)-N-(1-propyl) piperidine), a pharmacological tool to differentiate between the two different binding sites [5]. Moreover, molecular studies have shown that the binding site of repaglinide is different from that of glibenclamide and nateglinide [6].

Nateglinide

Nateglinide is a (N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine A-4166) phenylalanine derivative. Like repaglinide, also nateglinide binds competitively to SURs, inhibiting KATP channels and stimulating insulin secretion, but the pharmacodynamic properties of this molecule are unique in several aspects [7].

Comparative preclinical studies in vitro indicate that nateglinide inhibits KATP channels more rapidly, and with a shorter duration of action, than glibenclamide, glimepiride and repaglinide, and shows a greater degree of specificity for SUR1 over SUR2, as compared with glibenclamide and repaglinide. Also, the half-life of nateglinide on the receptor is approximately 2 s, much shorter when compared to that of repaglinide, which is ~3 min. In addition, the dissociation from the receptor is estimated to be 90 times faster than that of repaglinide, indicating a very short on-off effect of nateglinide on insulin release [8].

Foley *et al.* have demonstrated a sort of "glucose-sensitizing property" of nateglinide in *in vitro* experiments on rat β cells. In fact, unlike glibenclamide and repaglinide, the potency of nateglinide increases in the presence of glucose. The inhibition of KATP current is enhanced 16-fold when the glucose concentration is raised from 3 mmol/l to 16 mmol/l. Interestingly, the glibenclamide potency is much reduced under these conditions, whereas the potency of repaglinide is enhanced 4-fold only, which could explain the low incidence of hypoglycemia [8].

Moreover, pharmacodynamic studies in patients with T2DM have demonstrated that the administration of nateglinide (prior to meals) induces early phase insulin secretion and significantly reduces post-prandial hyperglycemia in a dose-dependent manner. Interestingly, insulin secretion was significantly greater when nateglinide was taken before a meal compared to nateglinide given in the fasted state or in response to just the meal [9].

Pharmacokinetic properties

Repaglinide

Repaglinide is rapidly absorbed after oral administration. The peak plasma concentration is reached 30-60 min after administration, plasma levels decrease rapidly and the drug is eliminated within 4-6 h. Its absorption is not affected by food, the bioavailability is 63% and the half-life is ~1 h [10].

Repaglinide has a small volume of distribution and is highly bound (more than 98%) to plasma albumin. Repaglinide is metabolized by the liver cytochrome P450 (CYP3A4) and eliminated rapidly throughout the biliary tract, without apparent accumulation in the plasma after a multiple dose [11].

Around 90% of the metabolites are excreted throughout the bile and only 8% can be traced in the urine. Only 2% of repaglinide is eliminated as unchanged and its metabolites are not biologically active and they do not have a blood glucose lowering effect.

In vitro studies have shown that substances which inhibit the enzyme CYP3A4, such as ketoconazole, anti-bacterial agents, steroids and cyclosporine, may reduce metabolism and increase repaglinide concentration, while drugs which induce CYP3A4, such as rifampicin, carbamazepine, and barbiturates, may accelerate repaglinide metabolism [11].

Nateglinide

Nateglinide is rapidly absorbed after oral administration from the gastrointestinal tract in a dose-dependent manner and the bioavailability of the drug is approximately 72% [12]. The optimal time of oral administration of nateglinide is before the meal; in fact absorption is more rapid when the drug is administered 0-30 min before meals [13]. Peak plasma concentrations are achieved within 1 h and the half-life is 1.8 h because it is rapidly eliminated from plasma. This short elimination half-life ensures no drug accumulation at any dose level. Nateglinide is metabolized mainly via the hepatic CYP2C9 and CYP3A4 isoenzymes of cytochrome P450 and eliminated primarily by the kidney. Twenty percent of a nateglinide dose is eliminated unmodified in the bile and 10% in the urine [12]. Nateglinide is also extensively bound to plasma proteins (98%) and has a relatively small volume of distribution [12].

Indications and dosage

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated the clinical importance of good glycemic control in the prevention of chronic vascular complications of T2DM, but also the limited long-term efficacy of drugs such as sulfonylureas, metformin, and acarbose, none of which proved capable of preventing a progressive increase in HbA_{1c} levels after an initial response [14]. The progressive nature of T2DM usually requires a combination of two or more oral agents, eventually followed and combined GLP-1 analogues, and finally insulin in the longer term.

The European Association for the Study of Diabetes-American Diabetes Association (EASD-ADA) Consensus Algorithm recommends the use of metformin as first line treatment in most patients, with the addition of other drugs to achieve adequate glycemic control, i.e. HbA_{1c} < 7%. Treatment choice should rely on the mechanism of drug action, efficacy and safety [15-17].

Post-prandial glycemia contributes to mean glucose and to HbA_{1c} levels, and therefore good control of post-prandial glycemia is a key element in the maintenance of HbA_{1c} levels < 7%. There is also evidence suggesting that post-prandial hyperglycemia could represent *per se* an important independent risk factor for diabetic macrovascular and microvascular complications in both T1DM and T2DM, also possibly because of increased oxidative stress [18-25].

Currently available hypoglycemic medications are all able to reduce HbA_{1c} level although to a different extent, but only a few of them can specifically reduce post-prandial glycemia [26-29].

Meglitinide analogues, acting on the pancreatic β cells, mimic somehow the early rise of insulin secretion after meal ingestion and reduce post-prandial hyperglycemia [2]. Clinical trials of nateglinide and repaglinide have shown efficacy and safety as monotherapy and in combination therapy in patients with T2DM.

The short-acting insulin secretagogues are well suited for patients with T2DM who would like to have a more flexible lifestyle and who have problems adhering to more rigid therapeutic regimes. In fact, administering short-acting insulin secretagogues immediately prior to meals increases patient compliance and flexibility in calorie intake and dietary adherence [26].

Both nateglinide and repaglinide have a good safety profile. Moreover, repaglinide is eliminated mainly via non-renal routes and can therefore be administered to patients with mild to moderate renal insufficiency and/or in whom one of the other second-line anti-hyperglycemic drugs is contraindicated [30].

In clinical trials in T2DM, repaglinide was usually administered at a dosage of 0.5-4 mg three times daily before meals as monotherapy or in combination with other agents and no dosage adjustment was necessary in mild and moderate renal impairment [31, 32].

During clinical development, and in clinical trials, nateglinide has been well tolerated. The insulin secretory response progressively increased after single doses of nateglinide up to 180 mg, and in another study, 120 mg was the maximally effective nateglinide dose for lowering glucose without the occurrence of hypoglycemia [9].

Clinical efficacy

Randomized, double-blind controlled trials have shown that nateglinide 360 mg/day significantly improves long-term glycemic control in patients with T2DM by reducing HbA_{1c} levels by 0.4-0.8% [33-35]. Compared with placebo, HbA_{1c} values are approximately 1% lower after nateglinide therapy [1, 34, 36]. When comparing repaglinide 1.5 mg/day and nateglinide 180 mg/day as monotherapy, in a 16-week study, the reduction in HbA_{1c} values from baseline was significantly greater for repaglinide than nateglinide (1.57% vs. 1.04%), and repaglinide had more pronounced effects on reducing fasting plasma glucose and glucagon secretion, with no differences in post-prandial glucose and insulin secretion [37].

Different studies have compared the efficacy of glinides and sulfonylureas. A study comparing the effects of 270 mg of nateglinide (n = 16) with 20 mg of gliclazide (n = 8) in a 12-week open label prospective study found that gliclazide was slightly more effective that nateglinide (HbA_{1c} 0.2% less in the gliclazide group) [38]. A small and short duration study (n = 47, 4 weeks duration) also showed sim-

ilar results comparing repaglinide 3.6 mg/day vs. gliclazide 54 mg/day on glycemic control and insulin secretion [39]. A double-blind, placebo-controlled trial compared the effects of repaglinide vs glimepiride therapy, with the dose of drugs optimized, showing the same reduction of HbA_{1c} and control of fasting glucose and post-prandial hyperglycemia after a 12-month treatment period [40].

A dose of 6 mg/daily of repaglinide showed an efficacy comparable to 2 g of metformin on fasting and integrated 6-h post-prandial measures of plasma glucose, triglycerides and serum free fatty acids in 96 non-obese T2DM patients during a 4-month crossover study [41]; in a 24-week multicenter study 360 mg of nateglinide was similarly effective to metformin 500 mg three times a day in terms of HbA_{1c} reduction (–0.8% in both groups) [34, 36].

When added to metformin, nateglinide at a dosage of 360 mg/day caused an HbA_{1c} reduction of approximately 0.4-0.8% [34, 36, 42], with a few studies reporting no differences between groups [43]. Metformin + nateglinide 540 mg/day was similarly effective to metformin + gliclazide 240 mg/day during a 24-week period (HbA_{1c} reductions of 0.41% and 0.57%, respectively). Notably, the metformin + nateglinide combination produced a more pronounced effect on post-prandial glucose than the metformin + gliclazide combination, and the latter had a better efficacy on fasting plasma glucose, with no differences in the rate of hypoglycemic events; however, when the study was extended to 1 year duration, the gliclazide group showed a slightly larger reduction of HbA_{1c} (–0.27 vs. –0.14) [44, 45]. When nateglinide + metformin was compared to glibenclamide + metformin, most of the studies have reported similar reduction of HbA_{1c} (1.0-1.5%), but some of them have reported a greater effect of the nateglinide + metformin combination (HbA_{1c} reduction 0.8% greater than the glibenclamide + metformin combination), confirming also that the nateglinide + metformin combination was more effective in reducing post-prandial plasma glucose, and the glibenclamide + metformin combination in improving fasting plasma glucose [46-49].

In a 24-week randomized clinical trial, the addition of 360 mg of nateglinide to 8 mg of rosiglitazone treated patients provided an additional reduction of HbA_{1c} of 0.8% [50].

Other studies have also demonstrated that glinides can be employed in combination with insulin. Repaglinide + bedtime NPH (n = 74) was compared to twice-daily NPH insulin (n = 71), revealing no differences in terms of HbA_{1c}, but at the same time they found a greater decrease in fasting plasma glucose in the NPH group (122 mg/dl vs. 144 mg/dl) [51]. In a 24-week randomized study, the combination of repaglinide + metformin + NPH (n = 12) had a higher decrease in HbA_{1c} when compared with groups of metformin + NPH (n = 12) and NPH + NPH (n = 13) (7.2% vs. 8.8% and 8.4%, respectively) [52]. In a 1-year randomized double-blind parallel study, repaglinide + biphasic insulin aspart (70/30) was similarly effective to metformin + biphasic insulin aspart to achieve a 1% HbA_{1c} reduction in non-obese diabetic patients [53]. Adding nateglinide before meals to once-daily insulin glargine in people with long-standing diabetes provides only a slight improvement in glucose control during the first part of the day, without any improvement on the overall glucose control [54].

Recently, the effect of glinides on the gastrointestinal incretin system has been investigated. It has been hypothesized that some of the beneficial actions of glinides may be indirectly mediated through dipeptidyl peptidase-IV (DPP-IV) inhibition. Dipeptidyl peptidase-IV is a ubiquitous enzyme that rapidly degrades the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Studies in humans have shown that nateglinide can inhibit DPP-IV, thereby increasing GIP levels [55], while other have reported no effect on the incretin levels [56]. The combination of nateglinide and GLP-1 improved glycemic control, increasing insulin and GLP-1 levels, as compared with nateglinide or GLP-1 alone, suggesting also that nateglinide had an inhibitory effect on the activity of DPP-IV or a stimulatory effect on GLP-1 secretion [57]. A study in rodents showed that promotion of GLP-1 release from intestinal L cells may be an additional mechanism by which nateglinide restores early-phase insulin secretion [58].

Role of glinides on the physiopathological abnormalities in type 2 diabetes mellitus

Multiple physiopathological abnormalities have been described in T2DM, including liver and muscle insulin resistance, beta and alpha cell dysfunction and incretin defect [59, 60]. The long-term efficacy of the available drugs is dependent on the impact of each one of them on the known physiopathological abnormalities of the disease. From this point of view, glinides mainly impact on the insulin secretion defect and possibly may have some effect on the increased glucagon secretion [37], and a few studies have suggested that glinides may also have some positive effect on the incretin system, by increasing the levels of GLP-1, especially when combined with GLP-1 [55, 57, 58].

Tolerability profile

Hypoglycemia

In most clinical trials, repaglinide and nateglinide treatment caused a low incidence of subjective symptoms of hypoglycemia [61-64].

Marbury *et al.* in a 1-year comparative trial demonstrated a similar rate of hypoglycemic events during repaglinide versus glibenclamide therapy and Madsbad *et al.* in a comparative study of repaglinide vs glipizide treatment did not demonstrate in either group any major hypoglycemic event and the number of patients experiencing minor hypoglycemia was similar in the repaglinide and glipizide groups [61, 62].

No severe hypoglycemic episodes occurred in patients treated with repaglinide plus metformin in a randomized study in naive T2DM patients, and combination therapy with repaglinide plus metformin resulted in fewer hypoglycemias than combination therapy with sulfonylureas [63, 64]. Repaglinide caused fewer hypoglycemias than glibenclamide also in elderly patients, as demonstrated by a small randomized crossover study in elderly patients [65].

Finally, repaglinide is safe and well tolerated in subjects with varying degrees of renal impairment. The incidence of hypoglycemic events did not differ between patients with renal dysfunction and healthy subjects who received repaglinide 2 mg three times daily [30].

Nateglinide is associated with a low risk of hypoglycemic events in placebo-controlled or active-controlled studies [49, 66].

Bellomo Damato *et al*., in a recent double-blind randomized study comparing nateglinide 120 mg three times daily with glyburide 5 mg once daily, demonstrated that nateglinide is associated with a lower risk of hypoglycemia than glyburide [66]. A double blind, multicenter, randomized study that aimed to assess the efficacy and tolerability of nateglinide alone or in combination with metformin in elderly patients with T2DM demonstrated that nateglinide monotherapy (120 mg) did not cause any serious hypoglycemic episodes. In the nateglinide/metformin arm there was one mild hypoglycemic episode compared with eight episodes in the glyburide/metformin arm [49].

Studies directly comparing repaglinide and nateglinide have been lacking and it is therefore not possible to assess their differences in term of clinical efficacy and safety [37, 67]. No major hypoglycemic episodes and no reported minor hypoglycemic events were found in the nateglinide group in a randomized, multicenter study, where patients were randomized to receive monotherapy with repaglinide (0.5 mg/meal, maximum dose 4 mg/meal) or nateglinide (60 mg/meal, maximum dose 120 mg/meal) for 16 weeks [37]. An open-label, parallel-group, randomized trial conducted to compare efficacy and safety of repaglinide vs. nateglinide in a combination regimen with metformin did not show any significant differences between the two treatment groups in terms of hypoglycemic event frequency [67].

Body weight

Body weight change was a secondary endpoint in several clinical trials with repaglinide and nateglinide [31, 68, 69].

In a multicenter, double-blind, placebo-controlled study, aimed to assess the efficacy and safety of repaglinide compared with placebo in type 2 diabetes patients, Goldberg *et al.* demonstrated only a small non-significant increase in body weight [31].

A multicenter, double-blind trial to compare the effect of repaglinide in combination with metformin in patients not controlled by metformin alone demonstrated an increase in body weight in the repaglinide group [68].

In another randomized, parallel-group study, comparing repaglinide and glibenclamide, the repaglinide group showed less weight gain than those treated with glibenclamide, over 1 year of treatment [62]. In a study aimed to compare the metabolic effects of add-on therapy with acarbose and repaglinide in patients treated with a sulfonylurea-metformin combination therapy, at the same glycemic control, the repaglinide group presented a significant increase in body weight [70].

Also nateglinide treatment was associated with a small body weight increase in most clinical trials. In the NAVIGATOR trial, conducted on subjects with impaired glucose tolerance, subjects treated with nateglinide did not show a significant increase in body weight as compared to the control group [71]. Only a modest increase in body weight was observed in diabetic patients receiving three fixed doses of nateglinide compared with placebo-treated patients [69].

Direct comparison trials of repaglinide and nateglinide to assess change in body weight have been few. In a multicenter study comparing monotherapy with repaglinide or nateglinide for 16 weeks, mean weight gain at the end of the study was 1.8 kg in the repaglinide group as compared with 0.7 kg for the nateglinide group [37].

Cardiovascular safety

Meglitinide stimulates insulin secretion by closing of KATP channels in β cells. KATP channels are ubiquitously present in extrapancreatic tissues including heart, central nervous system, skeletal muscle and smooth muscle. KATP channels are also abundant in both cardiomyocytes, where they are involved in the mechanisms of adaptation of the heart to ischemic stress, and arterial smooth muscle cells, regulating coronary blood flow [72].

Sulfonylureas and meglitinide analogues, binding to pancreatic β-cell KATP channels, may also bind to KATP channels of cardiomyocytes and vascular smooth muscle cells, possibly leading to impairment of ischemic preconditioning. Suggestions

about the possibility of worse clinical outcomes because of sulfonylureas treatment emerged from a *post-hoc* analysis of the DIGAMI study, but the UKPDS data did not support the suggestion of adverse cardiovascular effects of sulfonylureas [14, 73].

As reported above [5, 6], the meglitinide analogs bind to KATP channels at a different site and they have much shorter half-lives than do sulfonylureas, and this minimizes their potential negative effects on the heart. Repaglinide and nateglinide show different selectivity for KATP subtype. Nateglinide has a greater degree of specificity for SUR1 over SUR2, as compared with glibenclamide and repaglinide, and is up to 1000-fold more selective for the pancreatic KATP subtype than the cardiovascular subtype, while repaglinide is non-selective for the pancreatic KATP subtype [7, 8].

However, repaglinide treatment has not been shown to be associated with increased mortality and cardiovascular risk compared with metformin in a large cohort of diabetic patients with or without previous myocardial infarction [74]. In an open uncontrolled randomized study involving 112 patients with inadequately controlled type 2 diabetes not previously treated with oral hypoglycemic agents, the use of repaglinide was associated with improvements in cardiovascular risk profile [74, 75]. The NAVIGATOR study, conducted to evaluate the ability of nateglinide to reduce the risk of diabetes and cardiovascular events in people with impaired glucose tolerance, failed to demonstrate a reduction in diabetes incidence and cardiovascular events [71, 76].

Pancreatic β cell failure and meglitinide

Studies in β-cell line and rodent islets demonstrated that glybenclamide and tolbutamide may induce, Ca^{2+} dependently, β-cell apoptosis, and this finding was confirmed in a recent study conducted also in human islets [77, 78].

Although meglitinide analogues have similar effects to glibenclamide in terms of insulin secretion stimulation, it appears that nateglinide and repaglinide are less toxic for β cells, as widely reported in the recent review of Blickle *et al*. [79].

Animal studies also suggest that nateglinide reduces the risk of insulin depletion compared with glibenclamide [80]. Moreover, *in vitro* exposure of human islets to nateglinide did not increase the β-cell apoptosis rate and, consistent with this observation, repaglinide had no deleterious effects on β-cell survival [81, 82].

Conclusions

Nateglinide and repaglinide are effective in reducing post-prandial glucose excursion and HbA_{1c} levels by 0.8% to 1% in T2DM. We believe that the main role of glinides as a therapeutic option in T2DM is in combination with other drugs, since the treatment must be focused on the different mechanism of action of each drug. Glinides share some of the pharmacological properties with sulfonylureas, but show interesting differences with regards to their particular mechanism of action. Glinides stimulate insulin secretion with a very short half-life, which confers them the advantages of not causing excessive hypoglycemia, weight gain and chronic hyperinsulinemia, which are more common with sulfonylureas.

Acknowledgments

Annamaria Prioletta MD and her family passed away on December 25th, 2012 in a tragic car accident. This manuscript is dedicated to their memory.

We thank Tara Jean Zoll B.S. for correcting the scientific English form.

References

1. Dornhorst A. Insulinotropic meglitinide analogues. Lancet 2001; 358: 1709-16.
2. Landgraf R. Meglitinide analogues in the treatment of type 2 diabetes mellitus. Drugs Aging 2000; 17: 411-25.
3. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. Drugs 2001; 61: 1625-60.
4. Aguilar-Bryan L, Bryan J. Molecular biology of adenosine triphosphate-sensitive potassium channels. Endocr Rev 1999; 20: 101-35.
5. Fuhlendorff J, Rorsman P, Kofod H, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 1998; 47: 345-51.
6. Gromada J, Dissing S, Kofod H, Frokjaer-Jensen J. Effects of the hypoglycaemic drugs repaglinide and glibenclamide on ATP-sensitive potassium-channels and cytosolic calcium levels in beta TC3 cells and rat pancreatic beta cells. Diabetologia 1995; 38: 1025-32.
7. Hu S. Interaction of nateglinide with K(ATP) channel in beta-cells underlies its unique insulinotropic action. Eur J Pharmacol 2002; 442: 163-71.
8. Hu S, Wang S, Fanelli B, et al. Pancreatic beta-cell K(ATP) channel activity and membrane-binding studies with nateglinide: a comparison with sulfonylureas and repaglinide. J Pharmacol Exp Ther 2000; 293: 444-52.
9. Keilson L, Mather S, Walter YH, et al. Synergistic effects of nateglinide and meal administration on insulin secretion in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2000; 85: 1081-6.
10. Hatorp V, Huang WC, Strange P. Repaglinide pharmacokinetics in healthy young adult and elderly subjects. Clin Ther 1999; 21: 702-10.
11. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. Clin Pharmacokinet 2002; 41: 471-83.
12. Weaver ML, Orwig BA, Rodriguez LC, et al. Pharmacokinetics and metabolism of nateglinide in humans. Drug Metab Dispos 2001; 29: 415-21.
13. Luzio SD, Anderson DM, Owens DR. Effects of timing of administration and meal composition on the pharmacokinetic and pharmacodynamic characteristics of the short-acting oral hypoglycemic agent nateglinide in healthy subjects. J Clin Endocrinol Metab 2001; 86: 4874-80.

14. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 837-53.
15. Standards of medical care in diabetes 2013. Diabetes Care 2013; 36: S1-99.
16. Cicero AF, Tartagni E, Ertek S. Metformin and its clinical use: new insights for an old drug in clinical practice. Arch Med Sci 2012; 8: 907-17.
17. Derosa G, Maffioli P. Alpha-Glucosidase inhibitors and their use in clinical practice. Arch Med Sci 2012; 8: 899-906.
18. Bastyr EJ 3rd, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. Diabetes Care 2000; 23: 1236-41.
19. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006; 91: 813-9.
20. Folli F, Corradi D, Fanti P, et al. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: avenues for a mechanistic-based therapeutic approach. Curr Diabetes Rev 2011; 7: 313-24.
21. Folli F, Guzzi V, Perego L, et al. Proteomics reveals novel oxidative and glycolytic mechanisms in type 1 diabetic patients' skin which are normalized by kidney-pancreas transplantation. PLoS One 2010; 5: e9923.
22. Ihnat MA, Thorpe JE, Ceriello A. Hypothesis: the 'metabolic memory', the new challenge of diabetes. Diabet Med 2007; 24: 582-6.
23. Ihnat MA, Thorpe JE, Kamat CD, et al. Reactive oxygen species mediate a cellular 'memory' of high glucose stress signalling. Diabetologia 2007; 50: 1523-31.
24. Mannucci E, Monami M, Lamanna C, Adalsteinsson JE. Post-prandial glucose and diabetic complications: systematic review of observational studies. Acta Diabetol 2012; 49: 307-14.
25. Shiraiwa T, Kaneto H, Miyatsuka T, et al. Post-prandial hyperglycemia is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients. Biochem Biophys Res Commun 2005; 336: 339-45.
26. Bech P, Moses R, Gomis R. The effect of prandial glucose regulation with repaglinide on treatment satisfaction, wellbeing and health status in patients with pharmacotherapy naive type 2 diabetes: a placebo-controlled, multicentre study. Qual Life Res 2003; 12: 413-25.
27. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002; 287: 360-72.
28. Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II: Incretin-based therapy and beyond. Circulation 2008; 117: 574-84.
29. McGuire DK, Inzucchi SE. New drugs for the treatment of diabetes mellitus. Part I: thiazolidinediones and their evolving cardiovascular implications. Circulation 2008; 117: 440-9.
30. Marbury TC, Ruckle JL, Hatorp V, et al. Pharmacokinetics of repaglinide in subjects with renal impairment. Clin Pharmacol Ther 2000; 67: 7-15.
31. Goldberg RB, Einhorn D, Lucas CP, et al. A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. Diabetes Care 1998; 21: 1897-903.
32. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. Diabetes Care 2003; 26: 886-91.
33. Hollander PA, Schwartz SL, Gatlin MR, et al. Importance of early insulin secretion: comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. Diabetes Care 2001; 24: 983-8.
34. Horton ES, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care 2000; 23: 1660-5.
35. Rosenstock J, Shen SG, Gatlin MR, Foley JE. Combination therapy with nateglinide and a thiazolidinedione improves glycemic control in type 2 diabetes. Diabetes Care 2002; 25: 1529-33.
36. Horton ES, Foley JE, Shen SG, Baron MA. Efficacy and tolerability of initial combination therapy with nateglinide and metformin in treatment-naive patients with type 2 diabetes. Curr Med Res Opin 2004; 20: 883-9.
37. Rosenstock J, Hassman DR, Madder RD, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care 2004; 27: 1265-70.
38. Miwa S, Watada H, Ohmura C, et al. Efficacy and safety of once daily gliclazide (20 mg/day) compared with nateglinide. Endocr J 2004; 51: 393-8.
39. Zhang H, Bu P, Xie YH, et al. Effect of repaglinide and gliclazide on glycaemic control, early-phase insulin secretion and lipid profiles in. Chin Med J (Engl) 2011; 124: 172-6.
40. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. Clin Ther 2003; 25: 472-84.
41. Lund SS, Tarnow L, Frandsen M, et al. Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. Eur J Endocrinol 2008; 158: 35-46.
42. Marre M, Van Gaal L, Usadel KH, et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes Obes Metab 2002; 4: 177-86.
43. Weaver JU, Robertson D, Atkin SL. Nateglinide alone or with metformin safely improves glycaemia to target in patients up to an age of 84. Diabetes Obes Metab 2004; 6: 344-52.
44. Ristic S, Collober-Maugeais C, Cressier F, et al. Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results. Diabetes Obes Metab 2007; 9: 506-11.
45. Ristic S, Collober-Maugeais C, Pecher E, Cressier F. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. Diabet Med 2006; 23: 757-62.
46. Derosa G, D'Angelo A, Fogari E, et al. Effects of nateglinide and glibenclamide on prothrombotic factors in naive type 2 diabetic patients treated with metformin: a 1-year, double-blind, randomized clinical trial. Intern Med 2007; 46: 1837-46.
47. Derosa G, D'Angelo A, Fogari E, et al. Nateglinide and glibenclamide metabolic effects in naive type 2 diabetic patients treated with metformin. J Clin Pharm Ther 2009; 34: 13-23.
48. Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care 2005; 28: 2093-9.

49. Schwarz SL, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naive elderly patients with type 2 diabetes. Diabetes Obes Metab 2008; 10: 652-60.
50. Fonseca V, Grunberger G, Gupta S, et al. Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improves overall glycemic control. Diabetes Care 2003; 26: 1685-90.
51. Panelo A, Wing JR. Repaglinide/bedtime NPH insulin is comparable to twice-daily NPH insulin. Diabetes Care 2005; 28: 1789-90.
52. Civera M, Merchante A, Salvador M, et al. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. Diabetes Res Clin Pract 2008; 79: 42-7.
53. Lund SS, Tarnow L, Frandsen M, et al. Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial. BMJ 2009; 339: b4324.
54. Dashora UK, Sibal L, Ashwell SG, Home PD. Insulin glargine in combination with nateglinide in people with type 2 diabetes: a randomized placebo-controlled trial. Diabet Med 2007; 24: 344-9.
55. McKillop AM, Duffy NA, Lindsay JR, et al. Insulinotropic actions of nateglinide in type 2 diabetic patients and effects on dipeptidyl peptidase-IV activity and glucose-dependent insulinotropic polypeptide degradation. Eur J Endocrinol 2009; 161: 877-85.
56. Stephens JW, Bodvarsdottir TB, Wareham K, et al. Effects of short-term therapy with glibenclamide and repaglinide on incretin hormones and oxidative damage associated with postprandial hyperglycaemia in people with type 2 diabetes mellitus. Diabetes Res Clin Pract 2011; 94: 199-206.
57. Bell PM, Cuthbertson J, Patterson S, O'Harte FP. Additive hypoglycaemic effect of nateglinide and exogenous glucagon-like peptide-1 in type 2 diabetes. Diabetes Res Clin Pract 2011; 91: e68-70.
58. Kitahara Y, Miura K, Yasuda R, et al. Nateglinide stimulates glucagon-like peptide-1 release by human intestinal L cells via a K(ATP) channel-independent mechanism. Biol Pharm Bull 2011; 34: 671-6.
59. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; 58: 773-95.
60. Guardado-Mendoza R, Davalli AM, Chavez AO, et al. Pancreatic islet amyloidosis, beta-cell apoptosis, and alpha-cell proliferation are determinants of islet remodeling in type-2 diabetic baboons. Proc Natl Acad Sci USA 2009; 106: 13992-7.
61. Madsbad S, Kilhovd B, Lager I, et al. Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1-year multicentre study. Diabet Med 2001; 18: 395-401.
62. Marbury T, Huang WC, Strange P, Lebovitz H. Repaglinide versus glyburide: a one-year comparison trial. Diabetes Res Clin Pract 1999; 43: 155-66.
63. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes. Diabetes Obes Metab 2008; 10: 1167-77.
64. Wang W, Bu R, Su Q, et al. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naive to oral antidiabetes therapy. Expert Opin Pharmacother 2011; 12: 2791-9.
65. Meneilly GS. Effect of repaglinide versus glyburide on postprandial glucose and insulin values in elderly patients with type 2 diabetes. Diabetes Technol Ther 2011; 13: 63-5.
66. Bellomo Damato A, Stefanelli G, Laviola L, et al. Nateglinide provides tighter glycaemic control than glyburide in patients with type 2 diabetes with prevalent postprandial hyperglycaemia. Diabet Med 2011; 28: 560-6.
67. Raskin P, Klaff L, McGill J, et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care 2003; 26: 2063-8.
68. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 1999; 22: 119-24.
69. Saloranta C, Hershon K, Ball M, et al. Efficacy and safety of nateglinide in type 2 diabetic patients with modest fasting hyperglycemia. J Clin Endocrinol Metab 2002; 87: 4171-6.
70. Derosa G, Salvadeo SA, D'Angelo A, et al. Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double-blind, cross-over, clinical trial. Curr Med Res Opin 2009; 25: 607-15.
71. Holman RR, Haffner SM, McMurray JJ, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010; 362: 1463-76.
72. Quast U, Stephan D, Bieger S, Russ U. The impact of ATP-sensitive K+ channel subtype selectivity of insulin secretagogues for the coronary vasculature and the myocardium. Diabetes 2004; 53: S156-64.
73. Muhlhauser I, Sawicki PT, Berger M. Possible risk of sulfonylureas in the treatment of non-insulin-dependent diabetes mellitus and coronary artery disease. Diabetologia 1997; 40: 1492-3.
74. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison of glycaemic control and cardiovascular risk profile in patients with type 2 diabetes during treatment with either repaglinide or metformin. Diabetes Res Clin Pract 2003; 60: 161-9.
75. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 2011; 32: 1900-8.
76. Derosa G. Nateglinide does not reduce the incidence of diabetes or cardiovascular outcomes in people with impaired glucose tolerance and cardiovascular disease or risk factors. Evid Based Med 2011; 16: 7-8.
77. Efanova IB, Zaitsev SV, Zhivotovsky B, et al. Glucose and tolbutamide induce apoptosis in pancreatic beta-cells. A process dependent on intracellular Ca2+ concentration. J Biol Chem 1998; 273: 33501-7.
78. Maedler K, Carr RD, Bosco D, et al. Sulfonylurea induced beta-cell apoptosis in cultured human islets. J Clin Endocrinol Metab 2005; 90: 501-6.
79. Blickle JF. Meglitinide analogues: a review of clinical data focused on recent trials. Diabetes Metab 2006; 32: 113-20.
80. Laghmich A, Ladriere L, Malaisse-Lagae F, Malaisse WJ. Long-term effects of glibenclamide and nateglinide upon pancreatic islet function in normal and diabetic rats. Pharmacol Res 1999; 40: 475-82.
81. Kalbag JB, Walter YH, Nedelman JR, McLeod JF. Mealtime glucose regulation with nateglinide in healthy volunteers: comparison with repaglinide and placebo. Diabetes Care 2001; 24: 73-7.
82. Schumacher S, Abbasi I, Weise D, et al. Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. Eur J Clin Pharmacol 2001; 57: 147-52.