A review of nateglinide in the management of patients with type 2 diabetes

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Abstract: Impaired insulin secretion occurs early in the pathogenesis of type 2 diabetes mellitus (T2DM) and is chronic and progressive, resulting initially in impaired glucose tolerance (IGT) and eventually in T2DM. As most patients with T2DM have both insulin resistance and insulin deficiency, therapy for T2DM should aim to control not only fasting, but also postprandial plasma glucose levels. While oral glucose-lowering treatment with metformin and thiazolidinediones corrects fasting plasma glucose, these agents do not address the problem of mealtime glucose spikes that have been shown to trigger atherogenic processes. Nateglinide is a derivative of the amino acid D-phenylalanine, which acts directly on the pancreatic β-cells to stimulate insulin secretion. Nateglinide monotherapy controls significantly mealtime hyperglycemia and results in improved overall glycemic control in patients with T2DM by reducing glycosylated hemoglobin (Hb_{A1c}) levels. The combination of nateglinide with insulin-sensitising agents, such as metformin and thiazolidinediones, targets both insulin deficiency and insulin resistance and results in reductions in Hb_{A1c} that could not be achieved by monotherapy with other antidiabetic agents. In prediabetic subjects with IGT, nateglinide restores early insulin secretion and reduces postprandial hyperglycemia. Nateglinide has an excellent safety and tolerability profile and provides a lifetime flexibility that other antidiabetic agents could not accomplish. The aim of this review is to identify nateglinide as an effective "gate-keeper" in T2DM, since it restores early-phase insulin secretion and prevents mealtime glucose spikes throughout the day and to evaluate the results of ongoing research into its potential role in delaying the progression to overt diabetes and reducing its complications and mortality.

Keywords: nateglinide, type 2 diabetes mellitus, postprandial glycemia, impaired glucose tolerance, prevention of type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia, insulin resistance and β-cell dysfunction typified by loss of early (first-phase) insulin secretion (Weyer et al 1999). Chronic hyperglycemia is an established risk factor for the micro- and macrovascular complications associated with T2DM and especially for cardiovascular disease-the major cause of morbidity and mortality in subjects with diabetes (Lee et al 2000; Stratton et al 2000). However, epidemiological studies around the world have demonstrated a hidden risk factor associated with the overall diabetic mortality; in respect postprandial hyperglycemia (Khaw et al 2001). Indeed, the Diabetes Epidemiology Collaborative analyses of Diagnostic Criteria in Europe and Asia concluded that 2-hour postprandial plasma glucose levels (PPG) is a better predictor of premature death than fasting plasma glucose (FPG) (DECODE Study Group 2001; Nakagami and DECODE Study Group 2004).

Nowadays, postprandial hyperglycemia is widely recognised as the central feature of early diabetes and impaired glucose tolerance (IGT) (Home 2005). Postprandial hyperglycemia is caused primarily by the impairment of first-phase insulin secretion and the correction of this defect is an important determinant of long-term glycemic

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control (Dinneen 1995). It contributes significantly to the process of T2DM and, if uncontrolled, is an independent risk factor for macrovascular complications and associated mortality (Fonseca 2003). Moreover, as assessed by an ongoing clinical trial on the efficacy of nateglinide on prevention of T2DM in high-risk patients and cardiovascular outcomes, IGT may go undiagnosed in up to 31% of middle-aged patients at risk of developing cardiovascular diseases (Califf on behalf of the NAVIGATOR Trial Group 2003). Accordingly, the control of postprandial hyperglycemia is emerging as an important component of diabetes management (Ceriello 2005; Davies 2005).

In the normal individual the pancreatic β-cell responds in a biphasic manner to insulin secretagogues (such as glucose and amino acids). Essentially there is an early burst of insulin release within the initial 10 minutes and a second-phase characterized by a progressive increase in insulin secretion lasting up to several hours (Gavin 2001). The early burst of insulin secretion is critically important as it plays an important role in priming target tissues of insulin, especially the liver, responsible for normal glucose homeostasis following food uptake (Bratanova-Tochkova et al 2002). The loss of first-phase insulin secretion in response to glucose occurs relatively early in the development of T2DM and the early impairment of the functional integrity of plasma incretins, ie, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), has a major contribution to the β-cell deterioration and failure to suppress glucagon release post-meal (Laferrère et al 2007). As a result, an excessive prolonged insulin release from the pancreas will manage to eventually return glucose levels back to normal. Therefore, the patient is obligated to experience a prolonged period of hyperglycemia and hyperinsulinemia (Del Prato 2003).

Nateglinide is an insulinotropic agent that restores the physiological pattern of insulin secretion lost in T2DM in a transient and glucose-sensitive manner and thus can control glucose mealtime excursions. Nateglinide can be used in monotherapy, in order to control excessive mealtime glucose spikes early in the development of diabetes, or in combination with other agents that have complementary modes of action, such as metformin or glitazones, thus providing better overall chronic glycemic control by reducing Hb_{A1c} (Dunn and Faulds 2000).

In this review, we present data on the role of nateglinide as the "gate-keeper" of insulin secretion's early phase and additionally why and when to use such an early-phase insulin secretion agent in the treatment of T2DM. Moreover, ongoing data on its role in the management of prediabetes state are discussed.

Nateglinide and its effect on insulin secretory pathways

The exact mechanism by which insulin release is regulated to achieve euglycemia has not been completely established. However, pancreatic β-cells do respond to extracellular glucose through the generation of adenosine triphosphate (ATP) and the actions of ATP-sensitive K_{ATP} and voltage sensitive L-type Ca^{2+} channels in the β-cell membrane. Normally, ATP inhibits ATP-sensitive K^+ (K_{ATP}) channels, causing cell depolarization and the opening of voltage-dependent Ca^{2+} channels. As a result, the influx of Ca^{2+} triggers exocytosis and insulin release (McClenaghan et al 1999). K_{ATP} channels compromise a pore of inwardly rectifying K^+ channel subunits encased by sulfonylurea receptor subunits (SURs) with ATP-ase activity. Nateglinide binds competitively to SURs, thereby inhibiting K_{ATP} channels (Hu 2002). The interaction between nateglinide and K_{ATP} channels causes local depolarization of the plasma membrane. This is followed by an influx of calcium through the opening of the L-type Ca^{2+} channels and the stimulation of insulin secretion (Uto et al 2002).

Differences in the interactions with the K_{ATP} channels can potentially explain in part the contrasting pharmacological properties of each insulinotropic agent. In vitro, as well as in vivo studies have indicated that the plasma profiles for insulin secretion following administration of either repaglinide or glibenclamide are not reminiscent of the physiological patterns of insulin secretion (Laghmich et al 1999). They are characterized by a longer duration of action that produces a prolonged insulin secretion, which in its turn effectively reduces the ability of the pancreatic β-cell to mediate a moment-by-moment response to changes in blood glucose. Furthermore, this reduced responsiveness of the glucose feedback control system is handicapped by the relative insensitivity of both repaglinide and glibenclamide to glycemic status; the stimulation of insulin secretion is similar at low or high glucose levels (Hu et al 2000).

Nateglinide, as indicated by comparative studies, inhibits K_{ATP} channels more rapidly and with a shorter duration of action than both repaglinide and glibenclamide. This may be due to its greater degree of specifity for SUR1 over SUR2 receptors and the reduction of sustained depletion of islet cell insulin compared with sulfonylureas (Ball et al 2000). In addition, the short duration of action of nateglinide is glucose-dependent. The response of the K_{ATP} channel to

nateglinide is markedly lower during periods of euglycemia than at higher glucose concentrations. As nateglinide does not induce prolonged insulin release, it reduces the stress on the β-cell by eliminating the need for almost continuous insulin secretion. The clinical consequence of its short duration of action and its sensitivity to glycemic status is the decreased risk of hypoglycemia and potential pancreatic β-cell damage. Nateglinide has also been shown to enhance β-cell sensitivity to glucose in animal models without affecting basal insulin secretion. These preliminary observations support the view that, by increasing sensitivity to glucose, nateglinide may allow islet β-cells to avoid the unfavorable effects of chronic hyperinsulinemia (Ball et al 2004).

Lately, nateglinide has been reported to present a direct effect upon exocytosis of insulin independent of K_{ATP} channel function in the plasma membrane. This is achieved by targeting intracellular sites in the absence of K_{ATP} channel function. In this point of view, nateglinide has been shown to stimulate directly growth hormone exocytosis in rat pituitary cells and glucagon as well as insulin in pancreatic a- and β-cells, respectively (Bokvist et al 1998, 1999; Gromada et al 2002). This K_{ATP} channel-independent effect of nateglinide is increasingly thought to play an important role in the regulation of second-phase insulin secretion, which could provide considerable benefits in the therapy of subjects with T2DM. Most importantly, these effects of nateglinide were not accompanied by appreciable decline in cell viability or cellular insulin content (Maedler et al 2005). In conclusion, it may be sustained that nateglinide potentiates initiation and augmentation pathways for glucose-induced insulin release, suggesting likely effectiveness on both first- and second-phase insulin secretions.

Besides these benefits, nateglinide shows enhanced activity in an experimental in vitro model of the metabolic abnormalities associated with T2DM (ie, ATP depletion and the uncoupling of oxidative phosphorylation). The potency of nateglinide was increased by approximately 400-fold under these conditions, while the potency of glimepiride was increased 13-fold, that of glibenclamide was unchanged and that of repaglinide was decreased 10-fold (Hansen et al 2002). This implies that the structural determinants involved in nateglinide binding overlap with those of sulfonylureas. In contrast, the properties of repaglinide binding and inhibition differ from those of the sulfonylureas. This is of relevance in terms of other known differences in the mechanism of action of repaglinide and that of other insulin secretagogues. It is possible, although unproven, that the shared characteristics of the binding sites for nateglinide and sulfonylureas, demonstrated in this study, may explain these differences.

K_{ATP} channels subtypes are found not only in pancreatic β-cells, but also in coronary blood vessels (where they regulate coronary blood flow), in cardiomyocytes (where they aid the adaptation of the heart to ischemic stress) and in mitochondria (where they appear to help to "precondition" the heart to cope with prolonged ischemia). Thus, it is obvious that a further concern with therapeutic agents that influence K_{ATP} channels is their potential for affecting cardiac function. Patch-clamp techniques have been used to investigate the tissue selectivity of nateglinide for cardiac, β- and aortic cells in comparison with glibenclamide and repaglinide (Akiyoshi et al 1995; Hu et al 1999). Nateglinide demonstrates a significant degree of selectivity (up to 1000-fold) for the pancreatic K_{ATP} subtype over the vascular and the cardiac subtype (Chachin et al 2003). Glibenclamide shows only moderate pancreatic selectivity (10 to 20-fold) and repaglinide is non-selective (<2-fold). In other words, in contrast to repaglinide and glibenclamide, nateglinide would be less likely to cause detrimental cardiac effects via blockade of cardiovascular K_{ATP} channels than either of these agents. The selectivity of nateglinide for pancreatic K_{ATP} channels may confer additional advantages with regard to cardiovascular outcomes in patients with T2DM (Quast et al 2004).

Nateglinide pharmacokinetics

The molecule of nateglinide has a number of unique pharmacokinetic properties that contribute to its clinical utility in T2DM. First, it is rapidly and extensively absorbed from the small intestine after oral administration. Clinical studies in subjects with T2DM show absorption of nateglinide to be almost complete (≥90%) after oral administration, while its mean absolute bioavailability is estimated to be approximately 72%, indicating a modest first pass effect (McLeod 2004). A dose proportional (30–180 mg) rise in plasma levels follows oral administration with plasma concentrations peaking at approximately 1 hour post dose (Gribble 2001).

Although fasting status does not have a significant effect on overall plasma exposure, the existing data indicate that nateglinide should be administered before meals to maximize the rate of absorption (Kalbag et al 2000; Luzio et al 2001). The absorption profile of nateglinide does not appear to be significantly affected by meal composition and its plasma concentration-time curves are similar when administered shortly before a high fat, carbohydrate or protein meal (Karara et al 1999; Keilson et al 2000).

Nateglinide is extensively bound non-specifically to plasma proteins (primarily serum albumin) in the systemic circulation (>98%) and is distributed throughout the body. In vitro studies using nateglinide with a broad spectrum of drugs (furosemide, propranolol, captopril, nicardipine, pravastatin, glibenclamide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide or metformin) showed no binding interaction, suggesting a low potential for drug to drug interactions (Keilson et al 2000). However, the extensive binding to plasma proteins restricts distribution of nateglinide beyond the plasma volume, as indicated by the relatively low volume of distribution at steady state.

Nateglinide undergoes extensive metabolism prior to excretion. Less than 8% of unchanged drug is being excreted and its metabolites are rapidly eliminated with the major route of elimination being renal (~85% of dose) (Takesada et al 1996). There is no evidence for the accumulation of nateglinide or for any of its metabolites within the body (Weaver et al 2001).

Nateglinide pharmacodynamics

Pharmacodynamic studies in subjects with T2DM have demonstrated that the administration of nateglinide induces endogenous early phase insulin secretion in a physiological manner comparable with a bolus insulin dose. As the effect of nateglinide is specific to prandial insulin secretion, additional reductions in Hb_{A1c} may be achieved without risking the occurrence of hypoglycemic events between meals (Carroll et al 2002, 2003). The second phase of insulin release still occurs with nateglinide; however there is no extended insulin secretion (Barnett et al 2004).

An innovative, continuous method of plasma glucose measurement was recently used to evaluate nateglinide. Eighteen subjects with T2DM were monitored before and after 3 days of treatment with nateglinide which significantly reduced postprandial hyperglycemia following each meal and in addition lowered mean FPG levels (Abrahamian et al 2004). In subjects with IGT, a single-dose administration of nateglinide reduced postprandial hyperglycemia, without changing the area under the time–concentration curve of insulin secretion (Hirose et al 2002). Nateglinide may also improve insulin resistance, as measured by the homeostasis insulin resistance model, depending upon the degree of baseline insulin resistance (Shiba 2003).

Several studies have compared the pharmacodynamic effects of nateglinide and other insulin secretagogues. The efficacy of repaglinide and nateglinide in FPG, PPG excursion and early-phase insulin secretion was found to be similar, although the effect of repaglinide on Hb_{A1c} was stronger than that of nateglinide (Li et al 2007). Both nateglinide and repaglinide comparably improve insulin sensitivity and β-cell function but nateglinide achieves it with lower total insulin exposure (Hollander et al 2001; Abletshauser et al 2005).

The acute effect of nateglinide, glibenclamide and placebo on prandial plasma glucose, serum insulin, and C-peptide and glucagon excursions was studied in 15 subjects with maturity-onset diabetes of the young type 3 (MODY3). MODY3 is characterized by a defective insulin response to glucose and hypersensitivity to sulfonylureas. A low dose of nateglinide prevented the acute postprandial rise in glucose more efficiently and with less stimulation of peak insulin concentrations and hypoglycemic symptoms. Moreover, exercise did not induce hypoglycemia after nateglinide administration (Tinamaja et al 2006).

In a double-blind, multicenter study subjects with inadequate glucose control on maximal doses of metformin were randomized to additionally receive nateglinide or gliclazide. The nateglinide combination demonstrated better PPG control and the reduction from baseline in maximum PPG excursion was statistically significant in the nateglinide group only. Postprandial insulin levels were significantly higher with nateglinide (Ristic et al 2006). A study in drug-naïve patients given either nateglinide/metformin or glibenclamide/metformin combination treatment showed lower PPG excursions with nateglinide, while FPG concentrations were better with glibenclamide (Gerich et al 2005).

Control of body weight seems to be easier with nateglinide and in several studies, no significant increase in body weight was observed in patients treated with nateglinide despite the improved metabolic control. This was also valid when nateglinide was compared with metformin therapy (Fuchtenbusch et al 2000).

In subjects with T2DM, postprandial hypertriglyceridemia independently increases the risk of atherosclerosis, even in the presence of normal fasting triglyceride levels (Teno et al 2000). An acute effect of glibenclamide administration in humans demonstrated a reduction in total triglycerides and in triglycerides of intestinal origin (Skrapari et al 2001). Acute nateglinide-in comparison with glibenclamide-administration resulted in a greater suppression of postprandial lipemia in rats (Mine et al 2002) and in humans with T2DM (Mori et al 2004).

Data indicate that the suppression of postprandial non-esterified fatty acid levels during acute and chronic treatment with nateglinide results from the inhibition of endogenous lipolysis or lipid oxidation and lipogenesis (Dimitriadis et al 2004; Ceriello et al 2004). These effects on lipid profiles might contribute to an anti-atherogenic effect of nateglinide. A single dose of nateglinide was found to improve not only postprandial glycemia but also coagulation and fibrinolytic

activity in subjects with T2DM. This combined effect, if confirmed by a long-term study, might reduce cardiovascular risk in T2DM (Tentolouris et al 2005). Early insulin secretion following nateglinide administration can also suppress postprandial lipemia in subjects with newly diagnosed T2DM and improvements in insulin resistance over a short period of time seem to exert substantial influence on lipid parameters (Masumi et al 2006). Nateglinide not only ameliorates insulin resistance as well as insulin secretory defects but it decreases daily C-peptide excretion rate as well (Hazama et al 2006).

Nateglinide improves endothelial dysfunction in the postprandial state. This effect on endothelium may be important in the prevention of atherosclerosis in T2DM. A single dose of nateglinide administrated in subjects with T2DM abolished the deleterious effects of hyperglycemia on endothelial function (Shimabukuro et al 2004). However, further studies are needed to indicate that nateglinide ameliorates postprandial endothelial dysfunction in subjects with insulin resistance and to demonstrate the importance of postprandial metabolic regulation in the prevention of atherosclerosis.

Fasting versus postprandial hyperglycemia

The United Kingdom Prospective Diabetes Study (UKPDS 33 1998; UKPDS 49 1999) was the landmark study clearly to show that glycemic control is important for the prevention of micro- and macro-vascular complications in patients with T2DM. Postprandial hyperglycemic peaks seem to be prospective determinants of vascular damage in early T2DM, which can be prevented by improved glucose control in conjunction with adequate control of blood pressure and lipids. Thus, reaching a near-normal glycemic target is critically important (Standl et al 1996).

Although, the relationship between Hb_{A1c} and FPG as well as PPG is still controversial, postprandial hyperglycemia contributes to Hb_{A1c} values in subjects with T2DM, especially in patients with acceptable glycemic control (Monnier et al 2006 and Caputo et al 2001). In the UKPDS although concentrations of FPG were maintained over more than 5 years during the study, Hb_{A1c} showed a steady increase year after year. This indicates that control of FPG is insufficient to control Hb_{A1c} and that PPG peaks are a major source for Hb_{A1c} (UKPDS 49, 1999; Dimitriades et al 2004).

In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (Malmberg et al 1999), mortality after myocardial infarction was reduced with aggressive hypoglycemic treatment with insulin. Differences in glucose concentrations were associated with differences in Hb_{A1c}. Moreover, the normalization of blood glucose levels with insulin therapy improved the prognosis in critically ill patients, even if they did not previously had diabetes (Van den Berghe et al 2001). In conclusion, if prevention of macrovascular complications and Hb_{A1c} values near normal (ie, $<6.5\%$) are the goals of therapy, a good rationale for adequate control of postprandial hyperglycemia in diabetic patients should exist.

The UKPDS has substantiated that the loss of endogenous insulin secretion is the cause of the progression of T2DM. However, early insulinization was not advantageous over other forms of therapy. In recent years, the advent of polypharmacy has greatly strengthened the treatment of diabetes. Development of medications restoring early phase insulin-secretory defects is of clinical relevance in the managements of T2DM (American Diabetes Association 2001). Nateglinide can be used to reduce mealtime glucose excursions and Hb_{A1c} as monotherapy and in combination with metformin; its antidiabetic potential is similar to the combination treatment with glibenclamide and metformin. Additional substantiation of its long-term effect on improving life expectancy and reducing diabetic complications in subjects with T2DM is required (European Diabetes Policy Group 1999). Hb_{A1c} is the gold standard for assessing the impact of glucose control in terms of the occurrence and prevention of diabetic complications (Standl et al 2000). The DECODE study in Europe has indicated that in the context of Hb_{A1c} higher glucose excursions are a strikingly stronger predictor of cardiovascular risk than fasting hyperglycemia (DECODE study group 1999a, 1999b).

Metabolic phenotypes

Pharmacotherapy of subjects with T2DM is much individualized. The logical way to tailor antidiabetic therapy to the personal needs of subjects with T2DM and to ensure the best quality of life is to deliberate the disadvantages of pharmacotherapy on the one hand and to asses the specific metabolic characteristics of the individual patient on the other. In T2DM, four major metabolic phenotypes can be differentiated: postprandial versus fasting hyperglycemia, and insulin resistance versus insulin deficiency. However, the metabolic phenotype can alter along with the development and progression of the diabetes (American Diabetes Association 2005).

If the diagnosis is not delayed for years, T2DM often emerges predominantly as a postprandial disease. As a result, fasting hyperglycemia mostly points to a more advanced stage of insulin deficiency and a markedly increased hepatic glucose output. Insulin deficiency is particularly prominent

during the early phase of insulin secretion, leading to an insufficient suppression of hepatic glucose output after a meal and, hence, to postprandial hyperglycemia (Mitrakou et al 1992).

Insulin resistance seems to be a lifelong key problem in many patients with T2DM, even under treatment with insulin, and is aggravated by the modifiable factors of central obesity and physical inactivity. Insulin resistance is widely envisaged as the underlying denominator of the metabolic risk network consisting of hyperglycemia, hypertension and dyslipidemia (Reaven 1988).

Current treatment approaches to T2DM management

In the UKPDS (UKPDS 49 1999), loss of endogenous insulin secretion has been substantiated to cause the progression of T2DM and the reaching of a near-normal glycemic target is the golden goal, irrespective of the mode of therapy. The overall conclusion from this study was to treat T2DM as early as possible, and to escalate therapy, however, to more aggressively keep pace with the progressive disease, and take the use of insulin into consideration. The recent consensus statement by the American Diabetes Association and the European Association for the Study of Diabetes suggests initiation of metformin together with lifestyle changes as initial therapeutic approach to patients with T2DM (Nathan et al 2006). However, addition of either insulin secretagogues or glitazones or insulin is suggested when the HB_{A1c} goal is above 7%. The greatest advance in the treatment of T2DM in recent years is the advent of polypharmacy, initially suggested by the UKPDS. This synergy has been strengthened of late with the development of early-phase insulin secretion agents (Yki-Jarvinen 2000).

Modes to select antidiabetic drug treatment

The appropriate antidiabetic combination therapy is selected when the pros and cons of the available options are estimated in relation to the individual patient's coexisting morbidity, metabolic situation and preferred lifestyle. The therapy of choice is frequently based on the early combination therapy and the major determinants are body weight, the risk of hypoglycemia, and renal as well as cardiopulmonary function including heart failure (DeFronzo 2000). The stage of diabetes with its metabolic phenotype may influence the decision on the choice of therapy.

Antidiabetic regimens targeting mealtime hyperglycemia are a valuable monotherapy for early stages of glucose intolerance, or a constructive add-in treatment for later stages, delaying or even preventing the deterioration of β-cell function in the first instance and achieving optimum glycemic control. Enhancers of early-phase insulin secretion, short-acting insulinotropic agents, alpha glucosidase inhibitors, and rapid-acting insulin are already in use for the control of postprandial glycemia.

Current recommendations suggest starting combination therapy early, to maximize efficacy and to minimize side effects. This approach is suggested by the fact that type 2 diabetes results from a combination of both insulin resistance and insulin secretory defect. Additionally, antidiabetic drugs do not have a linear dose-effect relation; a medium dose of any antidiabetic agent will typically provide 70% to 80% of the maximum blood glucose lowering effect. Based on this notion, it is preferable to look for a synergistic combination therapy in case a medium dose monotherapy can not sufficiently reach the glycemic target, instead of titrating to effect resulting in a greater potential for side effects (Standl 1996).

Clinical efficacy of nateglinide

Nateglinide in preventing T2DM

A multicenter, double-blind, randomized study evaluated the metabolic effectiveness, safety and tolerability of nateglinide and identified a dose appropriate for use in a total of 288 subjects with IGT. Subjects received nateglinide (30, 60, and 120 mg) or placebo before each main meal. Metabolic effectiveness was assessed before and after an 8-week treatment and all adverse events were recorded. Nateglinide was safe and effective in reducing postprandial hyperglycemia in subjects with IGT. It concluded that, preprandial doses of 30 or 60 mg nateglinide can be considered appropriate to use for longer-term studies in order to determine whether a rapid-onset and reversible, insulinotropic agent can delay or even prevent the development of T2DM without raising the risk of hypoglycemia (Saloranta et al 2002).

The global NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial evaluates strategies to reduce or delay progression to diabetes and cardiovascular disease (CVD) in people with IGT. Its randomization is to nateglinide 60 mg versus valsartan 160 mg/day, versus both, versus neither. The study is carried out in two phases. In the first phase, designed to run for three years after the last subject is enrolled, the effect of nateglinide and valsartan on progression to diabetes will be evaluated. In the second, or 'extension' phase, the drugs' effects on cardiovascular disease will be evaluated. It is designed to study approximately 9,000 patients for up to 5 years. The end point for this trial is cardiovascular events, as well as conversion to diabetes (Callif on behalf of the NAVIGATOR Trial Group 2003).

The NAVIGATOR trial has already shown that an automatic assessment of glycemic status may improve unrecognized detection of IGT in people with risk factors for heart disease. During the initial screening of 43,509 subjects with the oral glucose tolerance test (OGTT) 37.5% had normal glucose tolerance (NGT), 12.2% had isolated impaired fasting glucose, 28.3% had isolated IGT and 22.0% had unrecognised diabetes. Retrospective analyses of studies using angiotensin converting enzyme (ACE) inhibitors have shown that they can favorably affect cardiovascular event rate or conversion to diabetes (Lindholm et al 2002; Strawn et al 2000). Data from the Decode Study Group has shown a strong association between postprandial glucose levels and cardiovascular event rates (DECODE Study Group 2001). This association has been noted across the spectrum of fasting blood sugars from the euglycemic to the diabetic range. Furthermore, it has been recently reported that treatment of insulin-resistant subjects with acarbose, a glucosidase inhibitor that interferes with glucose absorption and targets postprandial glycemia, is associated with a significant reduction in CVD (Chiasson et al 2003).

The NAVIGATOR trial is the only study powered to examine directly the potential for reducing the risk of CVD in addition to decreasing the risk of developing T2DM. There is an urgent need for a large-scale prevention program to target those people who have been identified as being at high risk of CVD and diabetes (Mazzone 2004). The final analysis of primary CVD events is expected to occur late in 2007, and it is anticipated that the results will be available in 2008.

Nateglinide in the management of T2DM

Patients suitable for nateglinide monotherapy are treatment-naïve patients and at an early stage of T2DM. Diabetic subjects with moderately elevated fasting plasma glucose and Hb_{A1c} levels, obese, elderly or with more severe diabetes, but who still have insulin secretion ability can also benefit from nateglinide monotherapy. Randomized, double-blind controlled trials have shown that nateglinide (120 mg three times daily before meals) significantly improves long-term glycemic control in patients with T2DM by reducing Hb_{A1c} levels by approximately 0.4%–0.8% (Horton et al 2000; Hollander et al 2001; Rosenstock et al 2002; Saloranta et al 2002). The improvements in overall glycemic control are explained by a dose-dependent effect on postprandial glucose excursions. Recent analysis from randomized-controlled trials suggests that nateglinide can be an alternative oral hypoglycemic agent of similar potency to metformin and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated. However, further data is needed to indicate what effect nateglinide will have on important long-term outcomes, such as mortality (Black et al 2007).

The efficacy and tolerability of the combination of nateglinide (120 mg t.i.d.) and metformin (500 mg t.i.d.) as initial treatment in drug-naïve patients with T2DM was examined in a 24-week trial that compared nateglinide, metformin and the combination therapy in 701 patients with baseline Hb_{A1c}between 6.8% and 11.0%. The two agents produced equivalent reductions in Hb_{A1c} of 0.8% at 24 weeks and had an additive effect in combination (Horton et al 2004). Indeed, 70% of patients treated with nateglinide plus metformin achieved an HbA1c level of $<7\%$ (Raskin et al 2003). Nateglinide (60 mg or 120 mg t.i.d.) was added to the therapy in patients with T2DM (n = 467) who were stabilised on high-dose metformin (1000 mg twice daily). After 24 weeks, both nateglinide doses significantly reduced Hb_{A1c} compared with placebo, with the greatest reductions occurring in patients with high baseline Hb_{A1c} levels (Marre et al 2002).

The effect of nateglinide on efficacy, tolerability and safety in elderly patients (n = 358) with T2DM (mean age up to 84 years) on diet alone or on metformin was assessed in a 12-week, parallel study. Nateglinide (120 mg) was given as either monotherapy in patients previously on diet alone or low-dose sulfonylureas (group 1) or as an addition therapy in patients on steady dose of metformin (group 2). Hb_{A1c} fell by a mean of 0.83% in group 1 and 0.67% in group 2. Forty four percent of patients in the first group and 34% in the second group achieved target of Hb_{A1c} <7.0 and 66% in group 1 and 59% in group 2 achieved of Hb_{A1c} $<7.5\%$ (Weaver et al 2002).

A double-blind, parallel, randomized, multicenter study compared the effects of nateglinide plus metformin with gliclazide plus metformin on glycemic control in patients with T2DM. Patients with inadequate glucose control on maximal doses of metformin were randomized to additionally receive for over 24 weeks nateglinide (n = 133) or gliclazide (n = 129). No significant difference was seen between the two groups in terms of Hb_{A1c}, the proportion of patients achieving a reduction of $Hb_{A1c} \geq 0.5\%$ or an end point Hb_{A1c} $<7\%$. The overall rate of hypoglycemia events was similar in the nateglinide group compared with the gliclazide group. However, the nateglinide combination demonstrated better postprandial glucose control and the postprandial insulin levels were significantly higher with nateglinide compared with gliclazide (Ristic et al 2006).

A 24-week, multicenter, double-blind, randomized study determined the effects of nateglinide added to rosiglitazone

monotherapy on glycemic control and on postprandial glucose and insulin levels in patients with T2DM. By selectively augmenting early insulin release and decreasing prandial glucose excursions, nateglinide produced a clinically meaningful improvement in overall glycemic exposure in patients with T2DM inadequately controlled with rosiglitazone. Therefore, nateglinide substantially improves the likelihood of achieving a therapeutic target of Hb_{A1c} <7.0% (Fonseca et al 2003).

Mathematical model data suggest that although drug treatment costs are increased by combination therapy, this cost is expected to be partially offset by a reduction in the costs of treating long-term diabetes complications (Ward et al 2004).

Recently, retrospective subgroup analyses from all completed nateglinide studies evaluated the impact of renal impairment (estimated creatinine clearance [Clcr] <60 mL/min per 1.73 m^2) and low baseline Hb_{A1c} (<7.5%) on comorbidity in patients with T2DM, and assessed the efficacy and safety of nateglinide monotherapy in these patients and in subgroups of patients over age 64 years with or without renal impairment. 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 (Del Prato et al 2003). Treating renal transplant recipients with nateglinide for two weeks significantly improved postprandial hyperglycemia, increased the insulin response following a standardized meal and was well tolerated (Voytovich et al 2007).

Recently, the effect of adding nateglinide to therapy with insulin glargine in adults (n = 55) with T2DM (Hb_{A1c}8.2 ± 1.0%), duration of diabetes 12.8 ± 6.0 years, duration of insulin treatment 6.0 ± 4.0 years) previously treated with insulin and with poor blood glucose control was determined in a 16-week, double-blind, placebo-controlled study. Addition of nateglinide before meals to once-daily insulin glargine in people with long-standing diabetes already requiring insulin therapy improved blood glucose control in the early part of the day after breakfast and lunch, but did not provide good control of blood glucose levels overall (Dashora et al 2007).

Conclusion: the position of an early-phase insulin secretion agent in the therapy of T2DM

Nateglinide, although is chemically distinct from sulfonylureas, conversely, from a more practical point it has many characteristics in common with the latest, as a very rapid and most short-acting insulin-releasing agent (Standl et al 2003). Nateglinide when given to subjects with T2DM just before meals decreases mealtime glucose excursions which improves overall glycemic control with a minimal risk of hypoglycemia. Compared with placebo, Hb_{A1c} values are approximately 1% lower after nateglinide therapy (Dornhorst 2001).

This non-sulfonylurea entity seems to be particularly appropriate for the control of postprandial hyperglycemia. It also, allows a more flexible lifestyle and the possibility to skip a meal without the risk of hypoglycemia that would be experienced with glibenclamide therapy. Conversely, an additional meal can be incorporated into the meal plan, preceded by an extra dose without worsening glycemic control (Hanefeld et al 2000).

According to current recommendations, metformin is the first-line therapy in the management of T2DM (American Diabetes Association 2006). Nateglinide may be an alternative option when the use of metformin is not advisable due to frequent contraindications and/or side effects (Horton et al 2000). Nateglinide could also replace favorably sulfonylureas in the early phase of T2DM, since nateglinide-induced insulin secretion may manage efficiently postprandial glycemia (Marre et al 2002).

Moreover, treatment with this insulin secretion agent does not incur chronic hyperinsulinemia, which can be advantageous in controlling body weight and avoiding the burden of otherwise occurring hypoglycemia. Hence, the use of nateglinide could be of benefit for elderly subjects (Weaver et al 2002).

Nateglinide since it does not contain a sulfonylurea moiety is also an excellent candidate for early combination therapy with other oral agents, in particular with metformin or glitazones. The blood glucose-lowering capacity of nateglinide is added to that of these medications and yields an overall potential Hb_{A1c} reduction of 1.8 to 2.5%. The UKPDS, however, has raised some controversy on the usefulness of this latter combination, as a result of a reportedly higher rate of cardiovascular complications compared with randomly maintained monotherapy with glibenclamide. Conversely, the cardiovascular complication rate was unusually low in the glibenclamide group (Hollander et al 2000).

Nateglinide could also be used in combination with either alpha-glucosidase inhibitors or glitazones. The combination with glitazones was shown to double Hb_{A1c} reduction compared with repaglinide monotherapy without significant weight gain, in contrast to the excessive weight increase

observed with the use of sulfonylureas and glitazones (Rosenstock et al 2002; Fonseca et al 2003). Nateglinide targets postprandial hyperglycemia via different mechanisms and should, therefore, be beneficial in combination with metformin or glitazones (Moses et al 1999).

In conclusion, the safety and convenience of nateglinide, coupled with its selective effect on postprandial hyperglycemia, makes it an attractive first-line, oral hypoglycemic monotherapy in newly diagnosed patients with T2DM that have near-normal fasting plasma glucose levels, are elderly, or who are unable to tolerate other oral hypoglycemic agents. It is also effective as combination therapy with metformin and glitazones for patients with more advanced disease requiring therapy to reduce both fasting and postprandial hyperglycemia.

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