The role of oral antidiabetic agents: why and when to use an early-phase insulin secretion agent in Type 2 diabetes mellitus

E. Standl¹, M. Füchtenbusch²

¹ Diabetes Research Institute Munich, Munich, Germany

² Department of Endocrinology, Academic Hospital Schwabing, Munich, Germany

Abstract

Evidence obtained in the 1990's strongly supports the notion that glycaemic control is important not only in Type 1 (insulin-dependent), but also in Type 2 (non-insulin-dependent) diabetes mellitus. Although measurement of HbA_{1c} is the standard for assessing the effect of glucose control in the occurrence and prevention of diabetic sequelae, more recent evidence indicates that other glucose parameters are also important. Postchallenge and postprandial hyperglycaemic peaks seem to be prospective determinants of vascular damage in early Type 2 diabetes. Currently, there is no overall accepted standard approach for the pharmacological management of Type 2 diabetes. The United Kingdom Prospective Diabetes Study has shown that reaching a near-normal glycaemic target is critically important and the pharmacotherapy of this progressive disease is difficult. Loss of endogenous insulin secretion has been substantiated to cause the progression of

Type 2 diabetes in the United Kingdom Prospective Diabetes Study. Early insulinization, however, was not advantageous over other forms of therapy. The advent of polypharmacy in recent years has greatly strengthened the treatment of this disease. This synergy has been extended of late with the development of early-phase insulin secretion agents. Two such agents, nateglinide and repaglinide, can be used to reduce meal-time glucose excursions and HbA_{1c} as monotherapy, and in combination with metformin; their antidiabetic potential is similar to the combination treatment with glibenclamide and metformin. Additional substantiation of their long-term effect on improving life expectancy and reducing diabetic complications in Type 2 diabetic patients is now required. [Diabetologia (2003) 46[Suppl1]:M30–M36]

Keywords Type 2 diabetes, hyperglycaemia, glucose control, blood pressure, lipids, oral antidiabetic agents.

The landmark United Kingdom Prospective Diabetes Study (UKPDS) and other studies have clearly shown that glycaemic control matters not only in Type 1, but

also in Type 2 diabetes [1, 2, 3]. Diabetic complications can be prevented by improved glucose control in this type of diabetes, and in conjunction with adequate control of blood pressure and lipids. Our ability, however, to reach the rather low long-term glycaemic targets suggested by the various international guideline groups for the treatment of Type 2 diabetes in recent years [4, 5] is, at best, limited in view of the complex and progressive nature of the disease. New treatment approaches are needed to attack the hyperglycaemic threat more appropriately and sufficiently in Type 2 diabetic patients. In this review, the present role of oral antidiabetic agents will be discussed and, in particular, why and when to use an early-phase insulin secretion agent, such as nateglinide and repaglinide, in treating Type 2 diabetes.

Received: 17 April 2001 / Revised: 2 August 2001

Published online: 18 December 2002

© Springer-Verlag 2002

Corresponding author: E. Standl, Diabetes Research Institute Munich, Kölner Platz 1, 80804, Munich, Germany, E-mail: eberhard.standl@lrz.uni-muenchen.de

Abbreviations: DECODE, Diabetes Epidemiology Collaborative Analysis of Diagnostic criteria in Europe; DIGAMI, diabetes mellitus, insulin glucose infusion in acute myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; MI, myocardial infarction..

Fasting versus postprandial hyperglycaemia

Although measurement of HbA_{1c} is still the gold standard for assessing the impact of glucose control in terms of the occurrence and prevention of diabetic sequelae, more evidence has accumulated indicating that other glucose parameters are also of importance [4, 5]. Postchallenge and postprandial hyperglycaemic peaks seem to be prospective determinants of vascular damage in early Type 2 diabetes [6, 7, 8] and even during impaired glucose tolerance (IGT), in particular in relation to cardiovascular disease [9, 10]. The Diabetes Epidemiology Collaborative Analysis of Diagnostic criteria in Europe (DECODE) and other epidemiological studies have indicated that higher glucose excursions during IGT are a strikingly stronger predictor of cardiovascular risk than fasting hyperglycaemia in the context of HbA_{1c} being in the non-diabetic range by definition [6, 7, 9, 10].

Postprandial hyperglycaemia also seems to contribute to the formation of HbA_{1c}. Postprandial blood glucose was more strongly correlated with HbA_{1c} than fasting blood glucose in a French study [11]. Targeting postprandial blood glucose in addition to fasting blood glucose during pregnancy led to a lower HbA_{1c} of approximately 1% [12]. Conversely, concentrations of fasting plasma glucose were maintained in the insulin arm of the UKPDS over more than 5 years during the second half of the study, yet HbA_{1c} showed a steady increase year after year [2]. This was reflected in the other treatment arms, suggesting postprandial glucose peaks were a major source for haemoglobin glycation in this situation. In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, aggressive antihyperglycaemic treatment with insulin reduced mortality after myocardial infarction (MI), in the short-term and long-term [13]. Differences in glucose concentrations were associated with differences in HbA_{1c} between these two randomised treatment groups. These inconsistencies were exclusively found in the non-fasting state. Overall, a good rationale for adequate control of postprandial hyperglycaemia in Type 2 diabetic patients exists, if prevention of macrovascular complications and near normal HbA_{1c} values (i.e. <6.6%) are the goals of therapy [4, 5, 8, 14].

The recently published American Diabetes Association (ADA) consensus report on postprandial blood glucose should also be mentioned in which, although acknowledging the increasing role of postprandial glucose, it was stated that there are still “insufficient data to determine the relative contribution of FPG (fasting plasma glucose) and PPG (postprandial plasma glucose) to HbA_{1c}. It appears that FPG is somewhat better than PPG in predicting HbA_{1c}, especially in Type 2 diabetes” [15]. Furthermore, the ADA report also concluded that for the time being, the contribution of postprandial plasma glucose to the long-term compli-

cations of diabetes mellitus is still controversial [15]. Although not proven, it could well be that over time, as the disease progresses from the phase of impaired glucose tolerance to chronic hyperglycaemia, the contribution of postprandial glucose to HbA_{1c} decreases relative to that of fasting glucose.

Metabolic phenotypes

Even in the post UKPDS era and the days of evidence-based medicine, pharmacotherapy of Type 2 diabetic patients has remained much more individualised than in Type 1 patients, where intensified insulin therapy is the treatment of choice. Deliberating the disadvantages of currently available treatments for pharmacotherapy on the one hand, and assessing the specific metabolic characteristics of the individual patient on the other, seems to be a logical way to tailor antidiabetic therapy to the personal needs of Type 2 diabetic subjects and to ensure best quality of life [16, 17]. Although there is always overlap, four major metabolic phenotypes can be differentiated: postprandial versus, fasting hyperglycaemia, and insulin resistance versus, insulin deficiency.

The metabolic phenotype can alter, however, along with the development and progression of the disease. Type 2 diabetes often emerges predominantly as a postprandial disease, provided the diagnosis is not delayed for years [18]. The potential role of postprandial hyperglycaemia as a cardiovascular risk factor has already been discussed. Fasting hyperglycaemia points to a more advanced stage of insulin deficiency and a markedly increased hepatic glucose output [19]. Strong insulin deficiency early in the progression of the disease could result in a misclassification of late-onset autoimmune (Type 1) diabetes in adulthood, but is certainly compatible with forms of Type 2 diabetes in various ethnic groups [20]. Insulin deficiency could be particularly prominent during the early phase of insulin secretion, even in the prediabetic IGT phase, leading to an insufficient suppression of hepatic glucose output after a meal and, hence, to postprandial hyperglycaemia [21]. Insulin resistance seems to be a lifelong key problem in many Type 2 diabetic patients, even under treatment with insulin, and is aggravated by the modifiable factors of central obesity and physical inactivity [22]. Insulin resistance is widely envisaged as the underlying denominator of the metabolic risk network consisting of hyperglycaemia, hypertension and dyslipidaemia [23].

Current treatment approaches to Type 2 diabetes management

Currently, there is no overall accepted standard approach to the pharmacological management of Type 2

Table 1. Mean efficacy of pharmacological treatment options in patients with Type II diabetes

Drug	Mean lowering of initial HbA _{1c} (%)
Alpha-glucosidase inhibitors	0.5–1.0
Biguanides	1.0–1.5
Glitazones	0.5–1.5
Sulphonylurea derivatives	1.0–1.5
Glinides	1.0–1.5
Insulin	1.0–2.0

diabetes. The UKPDS has shown how difficult the pharmacotherapy of this strikingly progressive disease can be and that reaching a near-normal glycaemic target is critically important, irrespective of the mode of therapy [24]. Loss of endogenous insulin secretion has been substantiated to cause the progression of Type 2 diabetes in the UKPDS [1, 2]. Early insulinization, however, did not seem to be advantageous over other forms of therapy. In the more obese (and probably more insulin resistant) subgroup of the UKPDS, metformin was the only therapy associated with a reduction of mortality in addition to a reduction of diabetic complications [25]. Hence, metformin treatment is widely recommended as first-line therapy in obese Type 2 diabetic patients, provided that contra-indications have been excluded. In addition, both glibenclamide and insulin as first-line therapy are also proven to reduce diabetic complications in both lean and obese Type 2 diabetic patients [1]. Still under debate, however, is the question as to whether this proven efficacy can be extrapolated to all insulin secretagogues. The sulphonylurea chlorpropamide also showed negative effects in the UKPDS; insulin therapy in this study was based on long-acting Lente insulin which has since been abandoned for other reasons [1].

Only a minority of patients in the UKPDS maintained their glycaemic target over 10 years, regardless of the initial randomly assigned pharmacotherapy, and in spite of additional therapy with other drug options [2]. The HbA_{1c} lowering capacity of all available drugs for the treatment of Type 2 diabetes as evaluated in randomised, placebo-controlled trials is limited at around 1% for most compounds and 2% at best (Table 1) [15, 16, 18, 26, 27, 28]. For example, between the less intensive treatment groups started exclusively on diet and the various drug treatment groups in the UKPDS, the difference in HbA_{1c} was 0.9% [1]. The overall conclusion from this study was to treat Type 2 diabetes 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. Treatment with antidiabetic drugs or insulin, as monotherapy, should be initiated if diet therapy and physical activity training pro-

Fig. 1. Synergy of treatment options for the therapy of Type II diabetes**Table 2.** Strategy of early combination therapy with oral agents

To maximize efficacy (medium dose yields 80% of the maximal effect)

To minimize side effects (e.g. weight gain, gastrointestinal discomfort or risk of hypoglycaemia)

grammes fail to maintain fasting plasma glucose concentrations of 6.0 mmol/l and HbA_{1c} values of less than 6.6% [4, 5].

The greatest advance in the treatment of Type 2 diabetes in recent years, is the advent of polypharmacy, initially suggested by the UKPDS [2]. This synergy (Fig. 1) has been strengthened of late with the development of early-phase insulin secretion agents. Our inclination is to start combination therapy early, to maximise efficacy and to minimise side effects (Table 2). Characteristically, 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 [15, 16]. 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 glycaemic target, instead of titrating to effect resulting in a greater potential for side effects.

Modes to select antidiabetic drug treatment

The analogy with antihypertensive drug treatment is remarkable. In the selection of the appropriate antidiabetic first-line therapy, the pros and cons of available options are estimated in relation to the individual patient's coexisting morbidity, metabolic situation and preferred lifestyle. After considering potential problems (Table 3), selection is based on the apparent metabolic phenotype (Table 4) and treatment usually started at low dose with subsequent slow adjustment to metabolic demands. In case of insufficient success, as a result of side effects or inade-

Table 3. Potential down sides of pharmacological treatment options in patients with Type II diabetes

Potential problem	Avoid or reconsider
Unwanted weight gain	SU, glin, glit, ins
GI symptoms	big, α -GI
Hypoglycaemia	SU, glin, ins
Impaired kidney function	big, SU
Impaired liver function	glin, glit, big, α -GI
Impaired cardio-pulmonary function	big, glit

NB, Oedema or lipid disorders may need further considerations; SU, sulphonylureas; big, biguanides; α -GI, α -glucosidase inhibitors; ins, insulin; glin, glinides; glit, glitazones

Table 4. Policy of selecting the appropriate oral antidiabetic compound according to the metabolic situation

Postprandial hyperglycaemia	alpha-glucosidase inhibitor, short acting sulphonylurea, glinide
Fasting hyperglycaemia	biguanide, long acting sulphonylurea, glitazone
Insulin resistance	biguanide, glitazone, alpha-glucosidase inhibitor
Insulin deficiency	sulphonylurea, glinide (insulin)

quate glycaemic control, an alternative option could be used.

Early combination therapy will frequently be the therapy of choice. Body mass index and the risks of hypoglycaemia, renal and cardiopulmonary function including oedema, are major determinants for the choice of treatment (Table 3). In contrast, the stage of the disease with its metabolic phenotype influences the decision on the choice of therapy (Table 4). If the problem is predominantly confined to the postprandial phase early in the disease, alpha glucosidase inhibitors, short-acting sulphonylureas, and enhancers of early-phase insulin secretion are good options for treatment, when potential adverse effects are also taken into account [15, 16, 29]. In more advanced stages, when fasting hyperglycaemia represents the main challenge, in the context of insulin resistance, metformin and glitazones are good candidates for drug treatment [15, 18, 29]. With increasing insulin deficiency, long-acting sulphonylureas and insulin therapy should be applied. Regulatory issues also play a role; European authorities have reserved some of the newer compounds, i.e. the glitazones, exclusively for combination therapy either with metformin or, if contraindications do not allow its use, with sulphonylureas. This and other restrictions, however, do not reflect specific evidence of negative research, but consider the avail-

ability of long-term results with metformin and sulphonylureas.

Profile and position of early-phase insulin secretion agents

At present, two so-called early-phase insulin secretion agents are available for therapy: nateglinide, a derivative of the amino acid D-phenylalanine, and repaglinide, a derivative of benzoic acid. Both are chemically distinct from sulphonylureas and recently, the term “glinide” has been used to describe that group of compounds. Although it is clear that these compounds are structurally dissimilar to sulphonylureas, they also have statistically significant differences to each other. Conversely, from a more practical point of view, glinides might be regarded as very rapid and most short-acting insulin-releasing agents which have many characteristics in common with sulphonylureas.

Nateglinide, like repaglinide and sulphonylureas, acts directly on the pancreatic beta cell to stimulate insulin secretion that is rapid, of short duration, and is dependent on ambient glucose [30, 31]. Experimental evidence shows that nateglinide restores early-phase insulin secretion even faster than the benzoic acid derivative, repaglinide, in diabetic animals [32]. Nateglinide given to Type 2 diabetic patients just before meals decreases mealtime glucose excursions which improves overall glycaemic control with a minimal risk of hypoglycaemia [33]. Compared with placebo, HbA_{1c} values are approximately 1% lower after nateglinide therapy [34, 35]. These new non-sulphonylurea entities seem to be particularly appropriate for controlling postprandial hyperglycaemia.

Both short-acting insulin secretion agents, nateglinide and repaglinide allow a more flexible lifestyle and the possibility to skip a meal without the risk of hypoglycaemia 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 glycaemic control. Unlike glibenclamide treatment, control of body weight seems to be easier with nateglinide [36]. In several randomised, placebo-controlled studies, no significant increase in body weight was observed in patients treated with nateglinide for up to 6 months, despite the improved metabolic control [34, 36, 37]. No differences in body weight were reported when nateglinide was compared with metformin therapy which has been shown to be associated with the lowest BMIs in the UKPDS [25]. Conversely, repaglinide therapy has been associated with some increase in body weight [15].

In summary, nateglinide and repaglinide offer good alternative options for first-line therapy when dietary therapy is not sufficiently effective, hyperglycaemia is

mainly confined to the postprandial state and the use of metformin is not advisable due to frequent contraindications and/or side effects. Nateglinide could also substitute favourably for sulphonylureas such as glibenclamide in this early phase of Type 2 diabetes, since nateglinide-induced insulin secretion is short lived. Moreover, treatment with this new insulin secretion agent does not incur chronic hyperinsulinaemia, which can be advantageous in controlling BMI and avoiding the burden of otherwise occurring hypoglycaemia [38]. Hence, the use of nateglinide could be of benefit for elderly subjects.

Such compounds which do not contain a sulphonylurea moiety are also excellent candidates for early combination therapy with other oral agents, in particular with metformin. The blood glucose-lowering capacity of nateglinide and repaglinide is completely additive to that of metformin, thus yielding an overall potential HbA_{1c} reduction of 1.8 to 2.5% comparable to the potency of combined glibenclamide and metformin [27]. 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 [39].

Nateglinide or repaglinide could also be used in combination with either alpha-glucosidase inhibitors or glitazones (Fig. 1). Combination with troglitazone was shown to double HbA_{1c} reduction compared with repaglinide monotherapy without significant weight gain, in contrast to the excessive weight increase of more than 6 kg reported for the combination of glibenclamide with troglitazone [40]. Alpha glucosidase inhibitors, repaglinide and nateglinide, all target postprandial hyperglycaemia via different mechanisms and should, therefore, be beneficial in combination; there is, however, no published evidence for this combination.

Multi-drug strategies and limits

Hard evidence for improving the outcome and reducing diabetic complications in Type 2 diabetic patients is currently only available for first-line therapy with either glibenclamide, insulin or metformin, the latter for obese patients [1, 25]. The variety of combination and multi-drug therapies is an obvious necessity in view of the immense difficulty of reaching and maintaining target metabolic control close to the normal range, i.e. to achieve an HbA_{1c} of less than 6.6%. With regard to outcome, however, no evidence is currently available showing the effective uses of these strategies on endpoints and reducing diabetic complications. Though it seems highly likely that diabetes-related morbidity and mortality will be re-

duced via glycaemic control achieved by combination therapy, one should not forget that the example combination of glibenclamide and metformin failed to achieve this goal despite improved metabolic control in the UKPDS [39]. Hence, more outcome-oriented long-term studies are mandatory in Type 2 diabetic patients. These should include both combination therapies (including the use of insulin) and monotherapy with the newer classes of antidiabetic agents.

For the time being it seems reasonable to add insulin to existing treatments, if oral combination therapy fails to achieve the target metabolic control. Moreover, this will also reduce HbA_{1c} values [41]. Alternatively, multiple dose insulin therapy should be discussed with the patient, although this strategy is not supported directly by outcome-based evidence [41]. A third option might be to extend oral treatment to triple therapy if target glycaemic control seems to be within reach by this approach [42]. Only a few studies using oral triple therapy and more triple therapy studies with the inclusion of insulin have been published. These usually indicate that the HbA_{1c}-lowering effect of the third drug is preserved.

Perspective

The availability of the early-phase insulin secretion agents nateglinide and repaglinide adds to our armamentarium to improve glycaemic control in patients with Type 2 diabetes. They can be used to reduce mealtime glucose excursions as monotherapy, and in combination with metformin; their antidiabetic potential is similar to the combined treatment of glibenclamide with metformin. Additional substantiation of the long-term effect of these innovative compounds to improve life expectancy and reduce diabetic complications in Type 2 diabetic patients is now required.

References

1. UK Prospective Diabetes Study Group (UKPDS) (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853
2. UK Prospective Diabetes Study Group (UKPDS) (1999) Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 281: 2005–2012
3. Standl E, Balletshofer B, Dahl B et al. (1996) Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia* 39: 1540–1545
4. ADA Position Statement (2001) Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care* 24 [Suppl 1]: S28–S32

5. European Diabetes Policy Group (1999) A desktop guide to Type 2 diabetes mellitus. *Diabet Med* 16: 716–730
6. The DECODE study group (1999) Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. European Diabetes Epidemiology Group. *Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe*. *Lancet* 354: 617–621
7. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M (2000) Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA_{1c} level. *Diabetes Care* 23: 1830–1834
8. Hanefeld M, Schmechel H, Schwanebeck U, Lindner J (1997) Predictors of coronary heart disease and death in NIDDM: the diabetes intervention study experience. *Diabetologia* 40 [Suppl 2]: S123–S124
9. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A (1999) Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 22: 920–924
10. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ (1999) Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 42: 1050–1054
11. Avignon A, Radauceanu A, Monnier L (1997) Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20: 1822–1826
12. Veciana M de, Major CA, Morgan MA et al. (1995) Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333: 1237–1241
13. Malmberg K, Norhammar A, Wedel H, Ryden L (1999) Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 99: 2626–2632
14. Standl E, Schnell O (2000) A new look at the heart in diabetes mellitus: from ailing to failing. *Diabetologia* 43: 1455–1469
15. American Diabetes Association (2001) Postprandial blood glucose. *Diabetes Care* 24: 775–778
16. Fuchtenbusch M, Standl E, Schatz H (2000) Clinical efficacy of new thiazolidinediones and glinides in the treatment of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 108: 151–163
17. Standl E (1996) New drugs for diabetes. In: Marshall SM, Home PD, Rizza RA (eds) *The Diabetes Annual* 10. Elsevier, Amsterdam, pp 225–249
18. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS (1997) Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 20: 1859–1862
19. DeFronzo RA, Goodman AM (1995) Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 333: 541–549
20. American Diabetes Association 2001: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 24 [Suppl]: 5–20
21. Mitakou A, Kelley D, Mookan M et al. (1992) Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326: 22–29
22. Nathan DM (1993) Long-term complications of diabetes mellitus. *N Engl J Med* 328: 1676–1685
23. Reaven GM (1988) Banting lecture. Role of insulin resistance in human disease. *Diabetes* 37: 1595–1607
24. Stratton IM, Adler AI, Neil HA et al. (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321: 405–412
25. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352: 854–865
26. Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT (1997) Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. The Glipizide Gastrointestinal Therapeutic System Study Group. *Diabetes Care* 20: 597–606
27. Hermann LS, Schersten B, Bitzen PO, Kjellstrom T, Lingard F, Melander A (1994) Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. *Diabetes Care* 17: 1100–1109
28. Moses R, Slobodniuk R, Boyages S et al. (1999) Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 22: 119–124
29. DeFronzo RA (2000) Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 133: 73–74
30. Hu S, Wang S, Dunning BE (1999) Tissue selectivity of anti-diabetic agent nateglinide: study on cardiovascular and beta-cell K(ATP) channels. *J Pharmacol Exp Ther* 291: 1372–1379
31. Hu S, Wang S, Fanelli B et al. (2000) Pancreatic beta-cell K(ATP) channel activity and membrane-binding studies with nateglinide: a comparison with sulfonylureas and repaglinide. *J Pharmacol Exp Ther* 293: 444–452
32. Dunning BE, Gutierrez C, Paladini S, Valentin MA, Foley JE (2003) Pharmacologic restoration of the early insulin response in pre-diabetic monkeys controls mealtime glucose excursions without peripheral hyperinsulinaemia. *Diabetologia* 46 [Suppl 1]: M22–M29
33. Keilson L, Mather S, Walter YH, Subramanian S, McLeod JF (2000) Synergistic effects of nateglinide and meal administration on insulin secretion in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85: 1081–1086
34. Horton E, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S (2000) Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 23: 1660–1665
35. Marre M, Whatmough I, Pongowski M, Guitard C (2000) Nateglinide added to metformin offers safe and effective treatment for type 2 diabetes. *Diabetes* 49 [Suppl 1]: A1517 (Abstract)
36. Hollander P, Schwartz SL, Gatlin MR et al. (2000) Nateglinide, but not glyburide, selectively enhances early insulin release and more effectively controls post-meal glucose excursions with less total insulin exposure. *Diabetes* 49 [Suppl 1]: A449 (Abstract)
37. Hanefeld M, Bouter KP, Dickinson S, Guitard C (2000) Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 23: 202–207

38. Merz M, Walter YH, Brookman L, Ma P, Gerich JE, McLeod JF (2000) Risk of delayed hypoglycemia is reduced with nateglinide compared to repaglinide. *Diabetologia* 43 [Suppl 1]: A714 (Abstract)
39. UK Prospective Diabetes Study Group (1998) UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. *Diabetes Care* 21: 87–92
40. Rosenstock J, Gatlin M, Mallows S, Bush C (2000) Nateglinide improves glycemic control alone and in combination with troglitazone in patients with type 2 diabetes. *Diabetes* 49 [Suppl 1]: A123 (Abstract)
41. Yki-Jarvinen H (2000) Comparisons of insulin regimes for patients with type 2 diabetes. *Curr Opin Endocr Diabet* 7: 175–183
42. Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch L (2001) Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pract* 51: 205–213