Efficacy and safety of nateglinide plus vildagliptin combination therapy compared with switching to vildagliptin in type 2 diabetes patients inadequately controlled with nateglinide

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Abstract

Aims/Introduction: To investigate the efficacy and safety of vildagliptin, a potent dipeptidyl peptidase-4 inhibitor, as add-on to nateglinide, compared to switching to vildagliptin in Japanese type 2 diabetes patients poorly controlled with nateglinide.

Materials & Methods: Forty patients inadequately controlled with nateglinide were randomized to the switching group (n=20, switching from nateglinide to vildagliptin) or combination group (n=20, nateglinide plus vildagliptin). A meal tolerance test was conducted at weeks 0 and 24.

Results: The mean changes in HbA1c from baseline to week 24 were -1.2±0.3 and –0.3±0.5% in patients of the combination and switching groups, respectively and the difference between the groups was statistically significant (p<0.001). The mean changes in glucose AUC0-180min from baseline to week 24 was -361±271.3 in patients of the combination group compared with 141±241.9 mmol·min/l in those of the switching group (p<0.001). The incidence of hypoglycemic events was low (three in combination group) and none of the patients developed severe hypoglycemia. Although the addition of vildagliptin to nateglinide did not significantly increase insulin secretion relative to glucose elevation after meal load (ISG0-180min:AUC0-180min insulin / AUC0-180min glucose)-in comparison with that in baseline, the mean ISG0-30min 24 weeks after addition of vildagliptin to nateglinide was significantly higher than that at baseline. In contrast, switching from nateglinide to vildagliptin reduced the mean
ISG$_{0-180\text{min}}$, relative to baseline.

**Conclusions:** The combination therapy of vildagliptin and nateglinide is effective and safe in Japanese type 2 diabetes and the improved glycemic control is due to augmentation of nateglinide-induced early phase insulin secretion.

This trial was registered with UMIN (ID000004010).

**Keywords:** DPP-4 inhibitors, glinides, insulin secretion.
Introduction

Early type 2 diabetes is currently considered an important target for drug therapy because large prospective and randomized studies proved that early and aggressive intervention to ensure proper glycemic control prevents both cardiovascular events and microvascular complications. The earliest determinant of progression to type 2 diabetes is loss of early insulin secretion, a defect that results in postprandial hyperglycemia, particularly in Asian population. In this regard, glinides, a class of rapidly acting insulin secretagogues, selectively enhances early meal-induced insulin secretion and thus improves mealtime glucose control. Consistent with the physiological nature of the categories of these drugs, the overall insulin exposure is relatively lower than that produced by sulfonylurea compounds in type 2 diabetes. However, glinides are not necessarily effective in all diabetic patients. These drugs are sometimes less effective in patients with advanced diabetes, especially those with persistent fasting hyperglycemia and those who are treated with these drugs for a long period of time. In such patients, many physicians select sulfonylureas as the next line antidiabetic agents, but these drugs do not effectively improve postmeal spike in glucose levels. In this regard, the combination of nateglinide and dipeptidyl peptidase-IV (DPP-IV) inhibitors [which exert their glucoregulatory actions through the prevention of incretin degradation, thus causing potentiation of GLP-1 and GIP actions], could potently lower both postprandial and fasting hyperglycemia. It has been reported that administration of DPP-IV
inhibitors strongly enhanced the potential of insulin secretion from insulin
secretagogue, including glinides in animals \(^{14}\) and sulfonylurea in healthy male
subjects \(^{15}\). The present study was designed to prove the therapeutic efficacy of
the combination strategy of nateglinide and vildagliptin, a stable, selective and
orally effective DPP-IV inhibitor \(^{16}\), in comparison with that of switching
strategy from nateglinide to vildagliptin.
Subjects and Methods

Patients

We screened type 2 diabetic patients who regularly attended Juntendo University Hospital between November 2010 and October 2011. Among them, we selected those with the following criteria: 1) on nateglinide treatment (90 mg thrice daily) for more than 1 year. 2) Older than 18 years of age, 3) HbA1c of >6.9% but <8.4%, 4) stable glycemic control with HbA1c variation <1.0% during the preceding 6 months, and 5) negative history of DPP-IV inhibitor, sulfonylurea, or alpha-glucosidase inhibitor therapy. Patients were also excluded if they had concomitant chronic diseases, such as anemia (hemoglobin ≤11.0 g/dl), kidney (plasma creatinine>1.50 mg/dl), liver (AST >80 IU/l or ALT >80 IU/l), or serious cardiovascular, pancreas or digestive organ disease; recent acute illness such as serious infectious disease or injury; progressive diabetic complication such as proliferative diabetic retinopathy, serious diabetic neuropathy, or other conditions such as current steroid therapy, or were suspected or confirmed to be pregnant. Heavy alcohol drinker or cancer patient was also excluded. The study protocol was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 17 and approved by the Ethic Review Committee of Juntendo University Hospital. All patients provided written informed consent and confirmed their willingness to attend this study. The equation between JDS and NGSP values of HbA1c has been defined as
previously reported 18, 19.

**Randomized clinical trial**

Among 65 inadequately controlled nateglinide-treated type 2 diabetic patients, 40 were invited to participate in an open labeled randomized controlled trial conducted at Juntendo University Hospital, Japan. The primary endpoints of the present study were 1) comparison of effects of combination of nateglinide to vildagliptin to those of switching from nateglinide to vildagliptin after 24 weeks, on glycemic control (HbA1c and AUC of serum glucose under standard meal loading test), and 2) comparison of the safety of the two regimens. The secondary endpoints included comparison of the effects of both therapeutic regimens on secretion of insulin and glucagon, serum lipid profile under standard meal load, and effects on blood pressure, and BMI.

After the 4-week screening period, eligible patients were randomized either to the combination therapy group [oral vildagliptin 50 mg twice daily and nateglinide 90 mg thrice daily just before each meal (n=20)] or to the switching group [vildagliptin monotherapy without nateglinide (n=20)] based on a computer-generated assignment. Patients were provided with recommendations for diet therapy during the screening period and after randomization. Restriction was imposed on patients taking any oral diabetic agents, insulin and other oral medications, such as blood pressure (BP)-lowering and lipid-lowering drugs for both groups, except for avoidance of the adverse effects such as hypoglycemia by
the attending physicians’ decision during the study.

At and after the screening visit, baseline laboratory data, including plasma adiponectin, BP, and body mass index (BMI), were determined for each subject. Standard meal loading test was also performed at weeks 0 and 24. Blood samples were obtained for the measurement of serum lipids (total cholesterol, HDL-cholesterol, and triglycerides) and HbA1c by standard laboratory techniques. BP was measured with a mercury sphygmomanometer. The baseline clinical characteristics of the subjects are shown in Table 1. Each patient was reviewed at least every 2 months, and the their general health, compliance with medications, laboratory data, blood pressure, and diet and exercise status were checked at each visit. At 24 weeks after the intervention, baseline laboratory data, BP, BMI, and standard meal loading test were determined again for each subject. The mean laboratory values for the observation period were calculated from the data obtained at each visit. Safety was also assessed by general physical examination, assessment of vital signs, clinical hematology and chemistry, urinalysis, and reporting of adverse events, in particular, hypoglycemic episodes.

**Standard meal loading test**

The subjects attended the Diabetes Unit at 09.00 hours after a 12-h fast (from 21.00 on the day before each test) and were administered 90 mg of nateglinide at baseline for both groups and 50 mg vildagliptin with or without 90 mg of nateliginide after intervention just before an oral standard-meal load
coordinated by the Japan Diabetes Society\textsuperscript{20}. The total energy content of the standard meal was 460 Kcal, with 56.5 g of carbohydrate, 18.0 g of fat, and 18.0 g of protein; with a total of 51.4 energy\% (E\%) from carbohydrate, 33.3 E\% from fat, and 15.3 E\% from protein. The meal had to be eaten within 15 min after receiving the drug. The subjects were at rest and sitting throughout testing.

An intravenous line was inserted into one forearm vein before drug administration and kept patent using 0.9\% NaCl for repeated blood sampling. Blood was drawn at 0, 15, 30, 60, 120, and 180 minutes after the meal. Time zero corresponds to immediately before drug administration. We measured glucose, insulin, glucagon, and lipids [triglycerides (TG), low density lipoprotein (LDL)-cholesterol, HDL-cholesterol, and total cholesterol] at 0, 15, 30, 60, 120, and 180 minutes; interleukin (IL)-6, total adiponectin, active GLP-1, and high sensitive C reactive protein (hsCRP) at 0, 30 and 120 minutes.

**Statistical analysis**

Data were analyzed with the use of PASW statistics (version 18 for IBM). All data are expressed as mean\(\pm\)SD unless otherwise indicated. To compare between-group differences during the course of the study, non-paired t-test was performed. To compare the differences between baseline and 24-week, paired t-test was performed. The area under the curve (AUC) was calculated by the trapezoidal method. A \(p\) value \(<0.05\) was considered statistically significant. Responder rates in each treatment group (percentage of patients achieving
end-point HbA1c <7.0%) were compared by the chi-squared test. A $p$ value of <0.05 denoted the presence of significant statistical difference.

**Results**

**Patients**

Figure 1 shows a flow chart of the trial profile of the present study. A total of 65 patients were recruited and 25 of them were excluded based on the criteria defined above. The remaining patients were randomly assigned to either the combination therapy group (combination group, n=20) or the switching to vildagliptin group (switching group, n=20). Seventeen of 20 (85%) patients of the combination group and 19 of 20 (95%) patients of the switching group completed the study. The reason for discontinuation in the combination group was absolutely mild hypoglycemia (3 cases) and that in the switching group was liver dysfunction, which improved after discontinuation of vildagliptin.

The baseline characteristics of the randomized patients are presented in Table 1. The two groups were well balanced at baseline, with a mean age, BMI, and HbA1c of 66±10 years, 25.0±4.1 kg/m$^2$, and 7.6±0.6% for the combination group, 63±13 years, 24.7±2.6 kg/m$^2$, and 7.5±0.6% for the switching group, respectively. Patients were predominantly males (>60%) with a mean disease duration of 11.8±5.6 years for the combination group and 11.6±9.0 years for the switching group.
**Efficacy (changes in glycosylated hemoglobin)**

Fig. 2a shows the serial changes in mean HbA1c during 24 weeks of treatment with vildagliptin-alone (switching group) and vildagliptin with nateglinide (combination group). At baseline, HbA1c was similar in the two groups (combination group: 7.6±0.6%, switching group: 7.5±0.6%). The pattern of decrease in HbA1c was different in the two groups: the mean HbA1c level decreased rapidly in the combination group from the start of the treatment until week 16, but decrease more gradually thereafter until the end of the treatment period. On the other hand, the mean HbA1c level was slightly but significantly lower after 24 week treatment, relative to the baseline in the switching group. The mean change in HbA1c (from baseline to endpoint, week 24) was -1.2±0.3% in the combination group and -0.3±0.5% in switching group and the difference was significant (***p<0.001, Fig. 2b). The target HbA1c (<7.0% at endpoint) was achieved by 82.3% of the patients in the combination group compared to 47.4% in switching group (p<0.05).

**Standard meal test**

Fig. 3 shows the serial changes in mean serum glucose concentrations before and after standard meal load (a) and mean fasting serum glucose level (b) at baseline and 24 weeks. The addition of vildagliptin to nateglinide significantly reduced glucose levels at 15, 30, 60, 120, 180 minutes compared with switching
from nateglinide to vildagliptin (8.4 and 10.0 at 15 minutes, ** p<0.01, 9.0 and 11.5 at 30 minutes, *** p<0.001, 9.8 and 13.4 at 60 minutes, ***p<0.001, 8.4 and 11.2 at 120 minutes, ***p<0.001 6.4 and 8.4 mmol/l at 180 minutes, **p<0.01 respectively) (Fig. 3a). There was a significant improvement in fasting glucose level in each group, relative to the baseline, but no significant difference between the groups (endpoint: switching group, 7.9±1.6; combination group, 7.4±1.4, baseline: 8.5± 1.5 and 8.4±1.6 mmol/l, respectively). However, a significant increase in the mean AUC of glucose from 0 to 180 minutes (AUC\textsubscript{0-180 min} glucose) was observed after switching from nateglinide to vildagliptin (baseline: 1852±303; endpoint: 1992±360 mmol • min/l, *p<0.05), while the mean AUC\textsubscript{0-180 min} glucose decreased significantly after the addition of vildagliptin to nateglinide (baseline: 1881±327; endpoint: 1520±256 mmol • min/l, ***p<0.001). The mean change in AUC\textsubscript{0-180 min} glucose from baseline to week 24 after the addition of vildagliptin to nateglinide was significantly lower than that observed in the switching group (-361±271 and +141±242 mmol • min/l, respectively, ***p<0.001, Fig. 3c). These results indicate that vildagliptin strongly improved both fasting and postprandial hyperglycemia when combined with nateglinide.

Fig. 4 shows serial changes in serum insulin (a) and the mean change in ISG\textsubscript{0 to 180 min} (AUC\textsubscript{0 to 180 min} insulin / AUC\textsubscript{0 to 180 min} glucose) from baseline to endpoint (b). The addition of vildagliptin to nateglinide did not significantly increase serum insulin levels at any time point (Fig. 4a) or in ISG\textsubscript{0 to 180 min}.
compared to baseline. In contrast, switching from nateglinide to vildagliptin significantly reduced serum insulin levels measured from 15 to 60 minutes, as well as mean in ISG0 to 180min, compared to baseline. The mean change in in ISG0 to 180min from baseline to week 24 after switching from nateglinide was significantly lower than that observed after addition of vildagliptin to nateglinide (-0.57±0.063 and +0.46±0.053 mIU/mmol respectively, **p<0.01, Fig. 4b). Although the combination improved glycemic control, it did not significantly change the mean in ISG0 to 180min relative to the baseline (baseline: 3.53±1.91; endpoint: 3.99±1.94 mIU/mmol). However, the combination of vildagliptin and nateglinide significantly enhanced early phase insulin secretion, reflected by in ISG0 to 180min (AUC0 to 30min insulin / AUC0 to 30min glucose), compared with the baseline (baseline: 3.04±1.36; endpoint: 3.83±1.85 mIU/mmol, *p<0.05). In case using delta insulin 0 to 30min /delta glucose 0 to 30min (termed as insulinogenic index) as early phase insulin secretion, the results were same as those in case using in ISG0 to 30min. The above changes resembled the original and specific features of nateglinide monotherapy on early phase insulin secretion.

Fig. 5 shows the serial changes in glucagon (a), and also the mean change in AUC 0 to 180min glucagon (b). During the 24-week treatment period, the AUC of glucagon tended to decrease from the baseline to endpoint in both groups, but the change was not significant. There was no significant difference between the two treatment groups with regard to the change in AUCs of glucagon (combination group: -481±3579; switching group: -1123±2801 μIU • min/ml, p=0.551).
Fig. 6 compares increment of plasma active GLP-1 concentrations after meal load (0 to 120 min) from baseline to endpoint in the combination and switching groups. The results showed no significant difference between the two groups. Similar changes were observed after 24-week treatment in postprandial adiponectin, IL-6 and hsCRP in the two groups (data not shown). A similar trend was noted for changes in lipid metabolism, except for significantly lowered fasting serum LDL-cholesterol in the combination group compared with the switching group (combination group: -13.0 ± 19.1; switching group: +1.7 ± 15.9 mg/dl, *p<0.05).

**Tolerability**

The overall incidence of adverse events was higher in the combination group than the switching group. The high incidence of adverse events in the combination group was due to higher incidence of hypoglycemia. Mild nausea and liver dysfunction were observed in one patient of the switching group. There were no serious adverse events during the treatment period in patients of either group.

Hypoglycemic events were observed in only 15% (3/20) of patients of the combination group, whereas none developed severe hypoglycemia. All hypoglycemic events occurred several hours after administration of vildagliptin during exercise. All hypoglycemia-related symptoms disappeared after reducing the dose of nateglinide.
There was no significant difference in changes in body weight between the two groups (combination group: 1.0±1.7; switching group: 0.4±1.6 kg, p=0.308). Furthermore, there were no major changes in hematological, biochemical and urinary parameters in the two groups, except for one patient from the switching group who developed a mild rise in liver transaminases.

**Discussion**

This study is the first to assess the efficacy and safety of vildagliptin used in combination with nateglinide in Japanese type 2 diabetes patients who were inadequately controlled with nateglinide.

Glinides are highly physiologic, mealtime glucose regulators\(^5\)\(^\text{-}8\),\(^17\), and effective and safe drugs for the treatment of early type 2 diabetics. However, their effects on insulin secretion are relatively weak compared with sulfonylureas, which produce potent and persistent stimulation of pancreatic insulin secretion. In this study, we compared the effects of the combination of vildagliptin and nateglinde on glycemic control.

Vildagliptin, as an add-on therapy to nateglinide (combination group) produced a significant and clinically meaningful reduction in HbA1c compared to switching to vildagliptin (switching group) (1.2±0.3% vs 0.3±0.5%; respectively, **p<0.001). HbA1c was reduced in each of the 20 patients of the combination group without exception. Among the patients of the combination group, 82.3% achieved HbA1c less than 7.0% at endpoint compared to 47.4% in
the switching group. These findings suggest that to accomplish strict glycemic control, it is better to continue nateglinide than to withdraw it when vildagliptin is prescribed as second line treatment for patients with type 2 diabetes who were inadequately controlled with nateglinide.

Nateglinide is an insulin secretagogue known to specifically stimulate early phase insulin secretion from beta cells\(^7,\ 8\). In the present study, the insulin secretion relative to glucose elevation after meal load (ISG\(_{0-180\text{min}}\):\text{AUC}_{0-180\text{min}}\) insulin / \text{AUC}_{0-180\text{min}}\) glucose) at 24 weeks after combination therapy of nateglinide and vildagliptin was significantly higher than that 24 weeks after switching from nateglinide to vildagliptin, although the difference relative to baseline was not significant. Interestingly, ISG\(_{0-30\text{min}}\), which reflects the ability of early phase insulin secretion, was significantly higher at 24 weeks after combination therapy than at baseline. These findings indicate that vildagliptin enhanced the effect of nateglinide on insulin secretion, as observed during monotherapy. Unfortunately, only a few reports have compared the effects of DPP-IV inhibitor on insulin secretion under stimulation with insulin secretagogues in diabetics. El-Ouaglidi et al.\(^{15}\) compared the effects of placebo, glibenclamide, vildagliptin or both on insulin secretion after 75 g oral glucose loading in 16 healthy subjects. Glibenclamide enhanced insulin and C-peptide responses and induced hypoglycemia. Vildagliptin alone did not enhance insulin secretory responses compared with placebo. Vildagliptin plus glibenclamide stimulated insulin and C-peptide responses from 30 to 240 min after glucose loading.
loading, compared with glibenclamide alone, although these differences were not significant. Asakawa et al.\textsuperscript{21} examined the efficacy of alogliptin, another DPP-IV inhibitor, on insulin secretion in diabetic rats with sulfonylurea-induced secondary failure. In their study, alogliptin exhibited significant improvement in glucose excursion with significant increase in insulin secretion. To our knowledge, only a few reports have been published on the effect of the combination of glinide and incretin-related drugs. Bell et al.\textsuperscript{22} reported the effects of exogenous GLP-1 on the hypoglycemic effects of nateglinide after intravenous glucose administration in type 2 diabetes. Plasma glucose responses were lowest and mean AUC\textsubscript{0-180min} insulin responses were highest with peak level at 15 min after intravenous glucose administration following the combination of nateglinide and GLP-1. In this report, plasma DPP-IV activity was lower and active GLP-1 concentration was higher following the combination than following GLP-1 or nateglinide alone, suggesting that nateglinide inhibits DPP-IV activity, as reported previously\textsuperscript{23,24}. The beneficial effects of the combination of nateglinide and vildagliptin may be indirectly mediated through DPP-IV inhibition and increased bioactivity of incretins. However, measurement of active GLP-1 concentration showed no significant differences between the combination and switching groups. These different results may be due to the single dose loading tests used in previous studies and the test after long medication with nateglinide in our study. Miura et al.\textsuperscript{25} have recently reported the effects of the combination of nateglinide and vildagliptin in an animal model\textsuperscript{25}. In their report,
treatment with nateglinide alone significantly stimulated early-phase insulin secretion and tended to improve postprandial glucose level in Zucker fatty rats. The combination of nateglinide with vildagliptin resulted in a more dramatic improvement in postprandial hyperglycemia, which resulted in decrease of AUC_{0-60min} insulin after meal load, compared with the control or nateglinide alone. Unfortunately ISG_{0-60min} was not calculated in that study though it could be presumed to have increased significantly.

The present study demonstrated that vildagliptin was well tolerated and that the overall incidence of adverse effects was comparable between the two groups. Furthermore, discontinuation due to adverse effects was only necessary in 15% of patients of the combination group and 5% of the switching group. The overall incidence of hypoglycemia was low in the combination group (15%), and each event was mild and precipitated by exercise. No episodes of severe hypoglycemia was encountered in this study, suggesting that vildagliptin can be added to nateglinide to achieve better glycemic control without increased risk of severe hypoglycemia. The rise in liver enzymes (more than three times increase in γGTP) in one patient of the switching group was transient and liver dysfunction improved after cessation of vildagliptin therapy.

Body weight increased from baseline to endpoint in both groups, with greater changes observed in the combination group than the switching one, although this was statistically insignificant. These findings are consistent with those of another study involving the combination of vildagliptin and sulfonylurea,
where body weight increased modestly in patients receiving vildagliptin 100 mg daily in combination with sulfonylurea\textsuperscript{26}. In that study, the increase in body weight in the vildagliptin plus glimepiride group was $1.3 \pm 0.3$ kg ($-0.4 \pm 0.3$ kg in placebo group), which is similar to those in Japan type 2 diabetes patients\textsuperscript{27}. In general, vildagliptin is considered neutral with regard to body weight even when combined with nateglinide, compared with the weight-promoting effects of thiazolidinediones\textsuperscript{28,29}.

Importantly, more than 80\% of the patients treated with the combination of vildagliptin and nateglinide achieved target HbA1c ($<7.0\%$). Overall, the combination treatment was associated with low incidence of hypoglycemia and no severe hypoglycemia.

In summary, vildagliptin add-on to nateglinide is efficacious and well-tolerated in the management of Japanese patients with type 2 diabetes who are inadequately controlled with nateglinide. This effect is mediated at least in part through a mechanism that enhances the favorable insulinotropic feature of nateglinide.

**Limitation of the present study**

The present study has certain limitations that need to be recognized. The study was conducted in a relatively small number of patients at a single institution. Further studies are needed to evaluate the long-term effects of vildagliptin with or without nateglinide on glycemic control and insulin secretion.
in larger number of patients and after more intensive education.

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**Figure Legends**

Fig. 1. Flow chart of the patient recruitment process.

Fig. 2. (a) Serial changes in HbA1c during the 24 weeks with vildagliptin or vildagliptin+ nateglinide (b) Mean changes in HbA1c at endpoint in the two treatment groups. #P<0.001, combination group vs switching group.

Fig. 3. (a) Serial changes in plasma glucose level at baseline with nateglinide and after 24 weeks with vildagliptin or vildagliptin + nateglinide after standard meal load. (b) Mean changes in fasting plasma glucose. ***P<0.001, baseline vs 24week in combination group. *P<0.05, baseline vs 24weeks in switching group. (c) Mean changes in AUCs of glucose from baseline to endpoint after standard meal load. #P<0.001, combination group vs switching group. ***P<0.001, baseline vs 24weeks in combination group. *P<0.05, baseline vs 24weeks in switching group.

Fig. 4. (a) Serial changes in plasma insulin level at baseline with nateglinide and after 24 weeks with vildagliptin or vildagliptin + nateglinide after standard meal load. (b) Mean changes in AUCs0-180min insulin / AUCs0-180min glucose (ISGs 0-180min) at endpoint in the two treatment groups. #P<0.01, combination group vs switching group. **P<0.05, baseline vs 24weeks in switching group. (c) Mean
change in ISGs 0-30min from baseline to endpoint. ***P<0.001, combination group vs switching group. *P<0.05, baseline vs 24weeks in combination group.
***P<0.001, baseline vs 24weeks in switching group.

Fig. 5. (a)Serial changes in glucagon at baseline with nateglinide and after 24 weeks with vildagliptin or vildagliptin + nateglinide after standard meal load. (b)Mean changes of AUCs0-180min glucagon after standard meal load from baseline to endpoint.

Fig. 6. Increment of plasma active GLP1 after standard meal load (0 to 120min) measured at baseline with nateglinide and after 24 weeks with vildagliptin or vildagliptin + nateglinide *P<0.001, baseline vs 24week in combination group. ***P<0.001, baseline vs 24week in switching group
Table 1 - Demographic and baseline characteristics (randomized population).

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<tr>
<td>Disease duration, years ^a</td>
<td>11.8±5.6</td>
<td>11.6±9.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) ^a</td>
<td>140.8±17.1</td>
<td>134.5±13.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg) ^a</td>
<td>82.1±11.0</td>
<td>77.7±11.2</td>
</tr>
<tr>
<td>Medications (n) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>6 (35.2)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>4 (23.5)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>4 (23.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>ARB, ACE</td>
<td>6 (35.2)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1 (5.9)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>0 (0)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>α-blockers</td>
<td>0 (0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Statins</td>
<td>9 (52.9)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>0 (0)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>1 (5.9)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td><strong>Anti-platelet agents</strong></td>
<td>4 (23.5)</td>
<td>4 (21.1)</td>
</tr>
</tbody>
</table>

^a Values are mean±standard deviation. ^b Values numbers of patients or (percentages).
Figure. 1 – Patient flow chart.

Assessed for eligibility (n=65)

Excluded (n=25)
- Unacceptable past medical history/concomitant diagnosis (n=2)
- Withdrawal of consent (n=23)

Randomized n=40

Vildagliptin 50 mg bid + nateglinide
Full analysis set (n=20)

Discontinued (n=3, 15%)
- AEs (n=3, 15%)
Completed (n=17, 85.0%)

Vildagliptin 50 mg bid
Full analysis set (n=20)

Discontinued (n=1, 5%)
- AEs (n=1, 5%)
Completed (n=19, 95.0%)
Figure 2

(a) vildagliptin

(b) vildagliptin + nateglinide

Mean HbA1c (%)

Mean change in HbA1c (%)

-1.23

0.295306421

-0.27

-1.6

-0.8

-1.2

-1.4

-1.6

-1.8

***

0 8 16 24

Time (weeks)
Figure 3.
Figure 4.
Figure 5.
Figure 6.