Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study

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Summary

Background Guidelines suggest setting individualised targets for glycaemic control in elderly patients with type 2 diabetes, despite no evidence. We aimed to assess the feasibility of setting and achieving individualised targets over 24 weeks along with conventional HbA_{1c} reduction using vildagliptin versus placebo.

Methods In this multinational, double-blind, 24 week study, we enrolled drug-naive or inadequately controlled (glycosylated haemoglobin A_{1c} [HbA_{1c}] ≥7·0% to ≤10·0%) patients with type 2 diabetes aged 70 years or older from 45 outpatient centres in Europe. Investigators set individualised treatment targets on the basis of age, baseline HbA_{1c}, comorbidities, and frailty status before a validated automated system randomly assigned patients (1:1) to vildagliptin (50 mg once or twice daily as per label) or placebo. Coprimary efficacy endpoints were proportion of patients reaching their investigator-defined HbA_{1c} target and HbA_{1c} reduction from baseline to study end. The study is registered with ClinicalTrials.gov, number NCT01257451, and European Union Drug Regulating Authorities Clinical Trials database, number 2010-022658-18.

Findings Between Dec 22, 2010, and March 14, 2012, we randomly assigned 139 patients each to the vildagliptin and placebo groups. 37 (27%) of 137 patients in the placebo group achieved their individualised targets by education and interactions with the study team alone and 72 (52·6%) of 137 patients achieved their target in the vildagliptin group (adjusted odds ratio 3·16, 96·2% CI 1·81–5·52; p<0·0001). This finding was accompanied by a clinically relevant 0·9% reduction in HbA_{1c} from a baseline of 7·9% with vildagliptin and a between-group difference of –0·6% (98·8% CI –0·81 to –0·33; p<0·0001). The overall safety and tolerability was similar in the vildagliptin and placebo groups, with low incidence of hypoglycaemia and no emergence of new safety signals.

Interpretation This study is the first to introduce and show the feasibility of using individualised HbA_{1c} targets as an endpoint in any type 2 diabetes population. Individualised glycaemic target levels are achievable with vildagliptin without any tolerability issues in the elderly type 2 diabetes population.

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Introduction

Type 2 diabetes mellitus is one of the most common chronic disorders in older adults and the number of elderly individuals with type 2 diabetes is growing worldwide, with a prevalence as high as 18–20% in adults older than 65 years.[1] Definitions of elderly, however, differ vastly and incorporate very different populations with respect to age, frailty status, and comorbidities, therefore each of these factors needs to be taken into account during identification of the most effective therapeutic targets and interventions.[2]

Clinical management of type 2 diabetes in elderly patients presents unique challenges because these patients have a higher burden of diabetes-related morbidity and mortality, microvascular and macrovascular complications, physical disability, cognitive impairment, and frailty.[3,4] Elderly patients with type 2 diabetes are more susceptible to the complications of hypoglycaemia[2,5] and are also frequently subjected to polypharmacy, which in turn increases the risks of drug interactions and adverse reactions.[6] Increasing age is associated with reduced renal function, which further limits therapeutic options in type 2 diabetes.[7] However, untreated or undertreated hyperglycaemia might also present risks of electrolyte abnormalities, dizziness, and falls.[6] In view of these complex treatment decisions, more than half of elderly patients with type 2 diabetes do not achieve conventionally recommended goals of glycaemic control (glycosylated haemoglobin A_{1c} [HbA_{1c}] <7%);[8–11] although, the validity of these targets is now being scrutinised.

In the UK Prospective Diabetes Study, reductions in cumulative microvascular and macrovascular events became apparent only after 9 years,[6,12] whereas in studies that used more aggressive targets,[13–15] macrovascular benefits were not realised at all. Therefore, the most recent set of guidelines emphasise individualisation of HbA_{1c} targets based on patients' characteristics and suggest less rigorous individualised care rather than tight glycaemic targets in el-

derly patients with limited life expectancy.[6,7,16] However, these guidelines largely use data extrapolated from patients younger than 70 years with type 2 diabetes because most randomised clinical trials exclude frail elderly patients with poor health status, leading to gaps in understanding about the most appropriate treatment regimens and the effects of glycaemic control in this population.[6,16] Furthermore, no trials using individualised targets or assessments of tolerability of any individualised treatments have been reported.

We aimed to assess the feasibility of setting and achieving investigator-defined individualised treatment targets for a period of 24 weeks in elderly patients with type 2 diabetes (drug-naive or inadequately controlled on oral agents), with the addition of a single oral agent. The drug of choice was the selective dipeptidyl peptidase 4 (DPP4) inhibitor vildagliptin because it has well documented efficacy and safety in elderly patients with type 2 diabetes.[17]

Methods

Study design and patients

In this 24 week, multicentre, randomised, double-blind, placebo-controlled study, patients were recruited from 45 outpatient centres in seven European countries (Belgium, Bulgaria, Germany, Finland, Slovakia, Spain, and UK). Patients aged 70 years or older with type 2 diabetes who were drug-naive or inadequately controlled, with HbA_{1c} levels of 7·0% or greater and 10·0% or less, fasting plasma glucose (FPG) of less than 15 mmol/L (270 mg/dL), and body-mass index of 19–45 kg/m^2 at screening (visit 1) were eligible. Patients who had taken no oral antidiabetic drugs (OADs) for at least 12 weeks before screening and no OADs for more than 3 consecutive months at any time in the past were regarded as drug-naive. Patients taking OADs at the time of screening were required to have had stable doses for at least 12 weeks before screening. The exclusion criteria included use of insulin treatment (>7 consecutive days) or incretin-based therapies in the preceding 12 weeks, use of corticosteroids within 8 weeks, or use of growth hormone within 6 months of the screening visit. Patients with acute metabolic diabetic disorders, myocardial infarction, coronary artery bypass surgery, or stroke within 6 months; unstable angina within 3 months; congestive heart failure (New York Heart Association classification of III or IV); malignancy within 5 years; or liver disease such as cirrhosis or hepatitis were excluded from the study. Substantial laboratory abnormalities including liver function tests, renal dysfunction as suggested by reduced glomerular filtration rate (<30 mL/min per 1·73 m^2), or positive hepatitis B or C tests also precluded participation.

This trial was done in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles laid down in the Declaration of Helsinki. An independent ethics committee or institutional review board at each research site reviewed the study protocol. Eligible patients were included in the study only after they had provided written informed consent.

Randomisation and masking

After a screening period of up to 2 weeks, eligible patients were randomly assigned to a treatment group (week 0) and followed up at four in-person visits (weeks 4, 12, 18, and 24) with an interim telephone contact at week 8. The randomisation list was produced by an interactive response technology provider (Cenduit, Durham, NC, USA) using a validated automated system that randomly assigned patients in a 1:1 ratio to receive either vildagliptin or placebo. The randomisation was stratified on the basis of the patient's background OAD treatment into drug-naive (no background OAD), sulphonylurea monotherapy, or all other background OADs (inclusive of sulphonylurea in a combination therapy). Patients, investigators, people doing the assessments, and data analysts were masked to the treatments from randomisation to database lock. The identity of the treatments was concealed by the use of study drugs that were identical in schedule of administration, packaging, labelling, appearance, taste, and odour.

Procedures

Patients in the drug-naive and other background OAD groups received vildagliptin (50 mg) twice daily or placebo, whereas patients in the sulphonylurea monotherapy group received vildagliptin (50 mg) once daily or placebo. Study drug dose adjustments or interruptions were not permitted. Patients remained on stable doses of OADs for the duration of the study. Study drug was discontinued and the patient withdrawn from the study if the investigator decided that continuation would result in a substantial safety risk for that patient. Insulin or any OAD (excluding incretin analogues and DPP4 inhibitors) could be used as rescue medication by the investigator at any time after randomisation if patients did not achieve a satisfactory therapeutic effect. However, efficacy data for patients receiving rescue medication were censored from the day after the rescue medication was started.

The two coprimary efficacy variables in this study were proportion of patients reaching their investigator-defined individualised HbA_{1c} target and the conventional HbA_{1c} reduction from baseline to week 24. Secondary efficacy parameters included change in FPG from baseline to study endpoint. We also explored investigator-defined treatment targets based on patient subgroups such as age, baseline HbA_{1c}, and frailty status. HbA_{1c}, FPG, bodyweight, vital signs, and liver function tests were measured at each study visit. Standard haematology and biochemistry laboratory assessments were done at screening and at weeks 0, 12, and 24, and urinalysis was done at weeks 0, 12, and 24.

All adverse events (AEs) and their severity, serious AEs (SAEs), and their presumed relation with the study drug were monitored and recorded at each study visit.

Particular attention was paid to safety areas thought to be of potential concern for DPP4 inhibitors[18] and elderly patients,[17] such as AEs associated with the liver, infections, pancreatitis, muscle, neuropsychiatric problems, lactic acidosis, skin or vascular problems, and cardiovascular or cerebrovascular events. We defined hypoglycaemia as symptoms suggestive of hypoglycaemia and a self-monitored plasma glucose measurement of less than 3·1 mmol/L. We defined severe hypoglycaemia as an episode that needed the assistance of another person or admission to hospital with or without a plasma glucose measurement of less than 3·1 mmol/L.

At baseline (visit 2), an individualised 24 week HbA_{1c} target was defined by the investigators for each of their patients, taking into account age of the patient, frailty status, comorbidities, and baseline HbA_{1c} values; most guidelines recommend using these factors to personalise treatments. Importantly, these investigator-defined individualised HbA_{1c} targets were based on the physicians' clinical judgment and local recommendations for glycaemic targets. Since this was not a treat-to-target protocol, the background medications of the patients were not titrated in an attempt to reach the individualised target. Frailty status of the patients was assessed with a modified version of a frailty phenotype proposed by Fried and colleagues.[19] Patients were regarded as frail if they had any two of the following three variables: unintentional weight loss (>4·5 kg or >5% loss of bodyweight in the past year), slow walking speed, and poor grip strength as measured by a dynamometer. All randomly assigned patients were educated about the management of their diabetes, the meaning of their individualised treatment targets, symptoms of hyperglycaemia and hypoglycaemia, possible triggers of hypoglycaemia, and appropriate treatment for events.

HbA_{1c} (measured by ion exchange high-performance liquid chromatography) and FPG samples were sent for analysis to a central laboratory (Covance, Geneva, Switzerland). Patients measured their blood glucose with one of several recommended calibrated home glucose monitors when they had hypoglycaemic symptoms and at other timepoints recommended by the investigator. Patients recorded the event in a glycaemic study diary, including the glucose value and any relevant associated information.

Statistical analysis

We expected a small sample size at most individual study centres, so all centres within the same country were combined to form a pooled centre. We analysed the proportion of patients achieving their individualised HbA_{1c} target at week 24 in each treatment group with a logistic regression model including terms for treatment, baseline HbA_{1c}, background OAD, and country. We then calculated the odds ratio (OR), defined as the odds of responding in one group divided by the odds of responding in the second group. We compared the change in HbA_{1c} from baseline to week 24 between patients assigned to vildagliptin and those assigned to placebo with an ANCOVA model that included terms for treatment, baseline HbA_{1c}, background OAD, and countries. We assessed the coprimary efficacy variables simultaneously for superiority compared with placebo with two-sided tests and a 5% significance level shared between the two variables, with 3·8% significance for the individualised treatment target and 1·2% for the difference in HbA_{1c}. The primary objective was fulfilled if either of the coprimary endpoints was met. We also analysed the risk ratio for the number of patients who reached the investigator defined HbA_{1c} target at study endpoint using a log linear regression model including terms for treatment, baseline HbA_{1c}, background OAD strata, and countries. We analysed the primary efficacy variables using data from the intention-to-treat population, which included all randomly assigned patients who received at least one dose of study drug and had at least one postbaseline efficacy measurement. We also did analyses based on the per-protocol set to assess the robustness of the conclusions.

We aimed to randomly assign about 280 patients (140 patients per group) to achieve a sample size of 238 completed patients (119 per group), assuming a drop-out rate of 15%. This sample size ensured 80% power at a 3·8% significance level for the ability to achieve the individualised treatment target, assuming about a

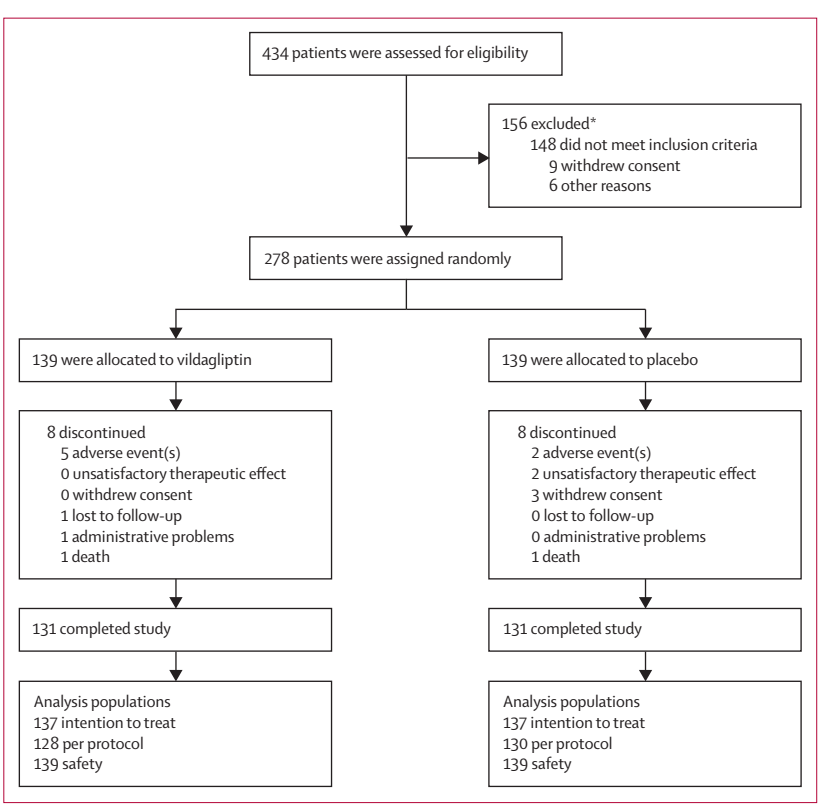

Figure 1: **Trial profile**
*Some patients were excluded for more than one reason.

	Vildagliptin (n=139)	Placebo (n=139)
Age (years)	75·1 (4·3)	74·4 (4·0)
Range	70·0–97·0	70·0–89·0
Men	73 (52·5%)	53 (38·1%)
Race		
White	135 (97·1%)	134 (96·4%)
Other	4 (2·9%)	5 (3·6%)
Systolic blood pressure (mm Hg)	137·0 (13·3)	137·5 (15·8)
Diastolic blood pressure (mm Hg)	76·8 (8·3)	76·9 (7·9)
Body-mass index (kg/m²)	29·1 (3·8)	30·5 (4·8)
HbA_{1c} (%)	7·9 (0·8)	7·9 (0·7)
Fasting plasma glucose (mmol/L)	9·6 (2·3)	9·9 (2·1)
Duration of type 2 diabetes (years)	12·2 (7·9)	10·6 (6·9)
Range	1·3–35·0	0·3–32·8
GFR (MDRD) (mL/min/1·73 m²)		
Normal (>80)	34 (24·5%)	31 (22·3%)
Mild (≥50 to ≤80)	86 (61·9%)	87 (62·6%)
Moderate (≥30 to <50)	19 (13·7%)	21 (15·1%)
Frailty status		
Yes	12 (8·6%)	14 (10·1%)
No	126 (90·6%)	123 (88·5%)
Missing	1 (0·7%)	2 (1·4%)

Data are mean (SD) or number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}. GFR (MDRD)=glomerular filtration rate estimated using the modification of diet in renal disease formula.

Table 1: **Baseline demographics and clinical characteristics**

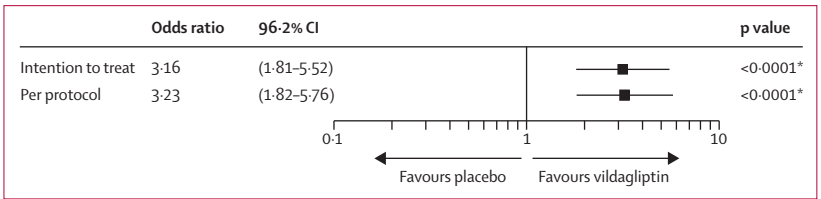

Figure 2: **Odds ratio for proportion of patients achieving individualised HbA_{1c} targets after 24 weeks**
Odds ratios, associated CI, and p values were calculated from a logistic regression model containing terms for treatment, baseline HbA_{1c} (centred by subtracting the overall mean baseline HbA_{1c} of all treatment groups), background oral antidiabetic drug strata, and pooled centres to compare the treatment effect. Squares show odds ratios for intention-to-treat analysis and per-protocol analysis; the lines show the 96·2% CI. Equivalent risk ratios for the number of patients who reached the investigator-defined HbA_{1c} target at study endpoint were 1·92 (96·2% CI 1·29–2·86; p=0·0013) in the intention-to-treat analysis and 1·91 (1·27–2·86; p=0·0017) in the per-protocol analysis. *Indicates statistical significance at two-sided 3·8% level.

19–22% percentage point difference in response rate between the vildagliptin and placebo groups. This sample size also ensured 90% power with a significance level of 1·2% to detect a between-group difference of half a standard deviation in HbA_{1c}. A difference of less than this amount, although of scientific interest, would not be clinically relevant. The endpoint for both primary efficacy variables was defined as the final available post-randomisation assessment obtained at any visit before or at the start of rescue medication use up to the visit at week 24.

We analysed the secondary efficacy variables with the same ANCOVA model as specified for the primary efficacy variable. Differences between vildagliptin and placebo were based on a two-sided 5% significance level. We used the last observation carried forward method to handle missing data due to early discontinuation or data censoring.

We produced a descriptive summary of the proportion of patients meeting individualised HbA_{1c} targets by treatment and baseline characteristic subgroups (age, baseline HbA_{1c}, frailty status). We also used a single multivariate model to analyse the effect of baseline characteristics on HbA_{1c} target setting on the intention-to-treat population. The model was based on the variables, which investigators were trained to follow, that should have affected target setting (target setting = frailty status [yes or no] + age [<75 or ≥75 years] + sex + duration of diabetes + screening HbA_{1c}).

We summarised safety data by treatment group for the safety set (including all patients who received at least one dose of study drug). Hypoglycaemia events were included in all AE summaries. We did all calculations with Proc Power procedure in SAS version 9.2.

The study is registered with ClinicalTrials.gov, number NCT01257451, and the European Union Drug Regulating Authorities Clinical Trials database, number 2010-022658-18.

Role of funding source

The sponsor of the study participated in the study design, data collection, data review, data analysis, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 22, 2010, and March 14, 2012, 434 individuals were screened and 278 participants were included in the study: 139 patients in each of the vildagliptin and placebo groups (figure 1). Most of the 156 patients excluded from the study either had unacceptable laboratory values (117 [75%]) or did not meet diagnostic or severity criteria (23 [15%]). Only eight (5·8%) patients in each group discontinued the study prematurely. The vildagliptin and placebo groups were similar for all patient demographic and background characteristics at baseline (table 1). The study cohort was representative of the overall elderly type 2 diabetes population[16] with a mean age of 74·8 years (SD 4·17; range 70·0–97·0), mean duration of diabetes of 11·4 years (SD 7·47; range 0·3–35·0), 213 (76·6%) patients with mild or moderate renal impairment, and 26 (9·4%) frail patients. Relevant medical history and comorbid disorders were similar in the two treatment groups with respect to hypertension (117 [84·2%] patients in the vildagliptin group *vs* 115 [82·7%] in the placebo group), dyslipidaemia (37 [26·6%] *vs* 29 [20·9%]), hypercholesterolaemia (22 [15·8%] *vs* 22 [15·8%]), hyperlipidaemia (36 [25·9%] *vs* 28 [20·1%]), myocardial ischaemia (22 [15·8%] *vs* 24 [17·3%]), peripheral neuropathy

(30 [21·6%] *vs* 36 [25·9%]), and osteoarthritis (27 [19·4%] *vs* 28 [20·1%]). As expected, almost all patients were using concomitant medications, with a substantial majority taking antihypertensive and lipid-lowering medications. Metformin and sulphonylureas were the most frequently used OADs; of the randomly assigned patients, nearly half were taking metformin, whereas a third were using sulphonylureas.

In this elderly cohort, the mean individualised HbA_{1c} targets set by the investigators were around 7·0% for both treatment groups, 0·9% (range –4·4 to –0·1) lower than the mean baseline HbA_{1c} of 7·9% in each treatment group. In the placebo group, 37 (27%) of 137 patients achieved their individualised targets as a result of education and interactions with the study team alone; this number was almost double, at 72 (52·6%) of 137, in the vildagliptin group. The adjusted OR of achieving the individualised target was 3·16 (96·2% CI 1·81–5·52; p<0·0001; figure 2). The number of patients reaching their individualised targets was higher in the vildagliptin group than in the placebo group, independent of their baseline characteristics (table 2). The risk ratios for the number of patients who reached the investigator-defined HbA_{1c} target at study endpoint were 1·92 (96·2% CI 1·29–2·86; p=0·0013) in the intention-to-treat analysis and 1·91 (1·27–2·86; p=0·0017) in the per-protocol analysis.

In terms of the conventional HbA_{1c} reduction from baseline to study endpoint, patients in the placebo group achieved a sizable change of –0·3% from a baseline of 7·9%. Vildagliptin consistently maintained HbA_{1c} at a lower level than did placebo (appendix) and resulted in a change of –0·9% from a baseline of 7·9%, with a statistically significant difference compared with placebo of –0·6% (98·8% CI –0·81 to –0·33; p<0·0001; figure 3). The study thus met both its coprimary endpoints. Analyses in the per-protocol study population showed very similar results for both primary endpoints. Both the vildagliptin and the placebo group showed a mean decrease in FPG at study endpoint; the difference between treatment groups of –0·9 mmol/L was statistically significant (p<0·0001; appendix). In terms of the effect of baseline characteristics on HbA_{1c} target setting, the only variables with a significant effect were sex (p=0·0258), with men set more aggressive targets than women, and HbA_{1c} (p<0·0001; appendix).

Overall safety and tolerability in the vildagliptin and placebo groups were generally similar in this elderly cohort (table 3). The number of patients with one or more AEs in the vildagliptin group (66 [47·5%]) was similar to that in the placebo group (63 [45·3%]). The number of patients reporting dizziness was numerically greater in the vildagliptin group than in the placebo group. Most AEs were assessed as mild or moderate and not related to the study drug. SAEs were reported for a low number of patients in both treatment groups. We noted no trends in the occurrence of SAEs, which were scattered across many system organ classes (appendix). AEs leading to discontinuation were few and similar in both treatment groups. Two patients died during the study, one in each study group, as a result of sudden cardiac death (in the vildagliptin group) and multiorgan failure (placebo). Neither case of death was suspected by the investigator to be related to the study drug. An analysis of specific safety topics of interest revealed no differences between the vildagliptin and placebo groups except that the proportion of patients reporting infections or infestations was a third higher in the placebo group (24 [17·3%]) than in the vildagliptin group (18 [12·9%]). We noted no reported cases of pancreatitis or clinically significant hepatic-related events.

The incidence of hypoglycaemic events was low overall: three (2·2%) of 139 patients in the vildagliptin group and one (0·7%) of 139 patient in the placebo group. All hypoglycaemic events occurred in patients using concomitant sulphonylureas. No severe hypoglycaemic events were reported in either group.

	Vildagliptin (n=137)	Placebo (n=137)
Age (years)		
<75	33/67 (49·3%)	22/86 (25·6%)
≥75	39/70 (55·7%)	15/51 (29·4%)
HbA_{1c} levels		
≤8%	46/83 (55·4%)	27/86 (31·4%)
>8%	26/54 (48·1%)	10/51 (19·6%)
≤9%	65/125 (52·0%)	34/128 (26·6%)
>9%	7/12 (58·3%)	3/9 (33·3%)
Frailty status		
Frail	5/12 (41·7%)	6/14 (42·9%)
Non-frail	67/124 (54·0%)	30/121 (24·8%)

Data are number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}.

Table 2: **Proportion of patients achieving individualised HbA_{1c} targets, according to baseline characteristics**

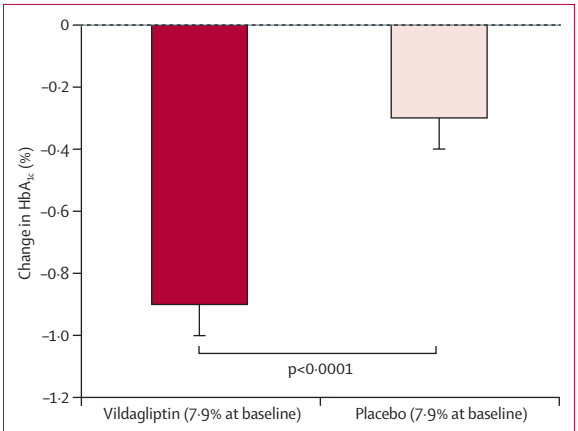

Figure 3: **Change in HbA_{1c} values from baseline to week 24 in the intention-to-treat population**
Bars show least squares mean; the lines from the bars show SE.

See Online for appendix

	Vildagliptin (n=139)	Placebo (n=139)
Overall*	66 (47·5%)	63 (45·3%)
SAEs†	8 (5·8%)	5 (3·6%)
Discontinuations due to AEs	6 (4·3%)	3 (2·2%)
Deaths	1 (0·7%)	1 (0·7%)
AEs (of any severity) in ≥5% of participants in any treatment group		
Dizziness	11 (7·9%)	3 (2·2%)
Headache	8 (5·8%)	4 (2·9%)
Nasopharyngitis	7 (5·0%)	7 (5·0%)
Any predefined risk‡	21 (15·1%)	24 (17·3%)
Hepatic-related AEs	0	0
Infection-related AEs	18 (12·9%)	24 (17·3%)
Pancreatitis-related AEs	0	0
Muscle-related AEs	1 (0·7%)	0
Neuropsychiatric-related AEs	1 (0·7%)	0
Lactic-acidosis-related AEs	0	0
Skin or vascular-related AEs	1 (0·7%)	0
Cardiovascular or cerebrovascular AEs	5 (3·6%)	3 (2·2%)

Data are number (%). AE=adverse event. *A patient with several occurrences of an AE on one treatment is counted only once in the AE category. †A detailed listing of the SAEs is available in the appendix. ‡Acute pancreatitis-related AEs, hepatic-related AEs, infection-related AEs, lactic-acidosis-related AEs, muscle-related AEs, neuropsychiatric-related AEs, and skin or vascular-related AEs were defined as events of predefined risk.

Table 3: **Treatment-emergent AEs in the safety analysis population**

No notable changes or abnormalities of any of the assessed vital-sign variables were recorded, and mean bodyweight hardly changed throughout the study in both treatment groups (79·9 kg at baseline and 79·8 kg at study endpoint in the vildagliptin group *vs* 80·7 kg at baseline and 79·7 kg at study endpoint in the placebo group; n=138 in each group).

Discussion

This study shows the feasibility of individualised treatment targets in clinical practice. Treatment guidelines for type 2 diabetes started proposing individualised care only after the results from landmark clinical trials[13–15,20] came into focus (panel). However, gaps exist in the knowledge with respect to absence of any large-scale intervention studies in older adults, patients with several comorbidities and geriatric syndromes, classification of older adults with increasing risk of mortality, and patients in dependent living situations.[6,16] These unique treatment challenges have not been particularly well addressed in clinical studies. Therefore, an understanding of the importance of assessing individualised target setting is needed, especially in a more fragile elderly population, as is comparing individualised target setting with conventional methods of assessing antihyperglycaemic therapies.

Our study introduced the unique endpoint of investigator-defined individualised HbA_{1c} targets in a pragmatic clinical trial setting, which parallels the guidelines for treatment of elderly patients with type 2 diabetes. The study population seemed to have well controlled type 2 diabetes with a mean baseline HbA_{1c} of 7·9%, and the mean investigator-defined individualised targets were about 0·9% lower than the mean baseline HbA_{1c}. This mean target of around 7·0% was substantially lower than we expected for this elderly population. All investigators were trained in the setting of individualised targets on the basis of clinical judgment, while including age, frailty status, comorbidities, baseline HbA_{1c}, and local treatment guidelines in their decision-making process. Despite this requirement to set a balanced target, the adherence to the mean 7·0% target suggests that investigators were greatly influenced by the conventional guideline-stipulated stringent HbA_{1c} target. This finding shows that synchronisation of the local and national guidelines with the global treatment guidelines[6,7,16] recommending less aggressive glycaemic targets for elderly patients with type 2 diabetes is needed, and calls into question the practical application of these global guidelines.[7,16] We believe, however, that part of the issue might lie in the novelty of this study; despite guidelines, recommendations, and the study-specific training provided, no evidence for less aggressive targets is available.

After 24 weeks of treatment, a quarter of the patients achieved their individualised targets by simple education and interactions with a study team focusing on personalised care rather than target number chasing. After adjustment for baseline characteristics, addition of vildagliptin increased the ability to achieve the individualised targets by more than three times without major tolerability issues. The vildagliptin group consistently had a higher proportion of patients who had reached their individualised targets than did the placebo group, irrespective of age, baseline HbA_{1c}, and frailty status. During the course of this study, patients given vildagliptin also achieved clinically relevant reductions in HbA_{1c} (–0·9%) and FPG. Our findings support previously reported efficacy of vildagliptin in elderly patients with type 2 diabetes.[17,21,22] We should emphasise that physicians set rather aggressive targets even in these relatively well controlled elderly patients. Thus a substantial proportion of patients achieving their individualised HbA_{1c} targets were also very close to the conventional target.[7]

As expected, most patients in our study had a long duration of diabetes, had several diabetes-related or other comorbidities, and needed polypharmacy at baseline. Most of the patients also had mild or moderate renal impairment. Despite these challenging factors, the safety and tolerability of vildagliptin in this cohort was similar to that of placebo. Most of the reported AEs and SAEs were isolated events, generally expected in an elderly type 2 diabetes population, and did not show any particular clinically relevant trends. Although the

vildagliptin group had numerically more AEs suspected to be drug-related or that led to discontinuation than did the placebo group, most AEs were mild to moderate, occurred at a far lower frequency than expected, and seemed to be less frequent than reported in other studies with DPP4 inhibitors,[23] although such a comparison does have its limitations. Our study further corroborates the safe profile of vildagliptin reported in two separate pooled analyses of vildagliptin studies in elderly patients with type 2 diabetes.[17,21]

Hypoglycaemia and its related effects are of special concern in elderly patients with type 2 diabetes. This population of patients has fewer adrenergic symptoms such as sweating and tremor than do younger patients with diabetes, and more neuroglycopenic symptoms such as confusion, which make hypoglycaemia more difficult to recognise.[2,6] Hypoglycaemic episodes tend to be more severe in elderly patients, possibly due to impaired counter-regulatory response, which can lead to serious events such as falls and fractures and potentially increase cardiovascular risk.[3] In our study, despite the stringent and clinically significant glycaemic control, the overall incidence of hypoglycaemic events was low and similar in both treatment groups and no severe hypoglycaemic events were reported. All patients who had hypoglycaemic episodes were taking high doses of sulphonylureas. Our study supports the very low incidence of hypoglycaemia reported previously with vildagliptin in the elderly population[17,21,22] or in other highly susceptible patient populations such as patients with moderate or severe renal impairment.[24]

In our study we used broad inclusion criteria consistent with existing labelling for vildagliptin to reflect a real-world setting, which ensured that we had study patients that seemed mostly representative of the overall elderly type 2 diabetes population who were likely to be prescribed vildagliptin irrespective of their participation in this study. However, the small sample size and short study duration were potential limitations of this study. We also did not measure compliance with polypharmacy, which could potentially affect such an elderly population. A further limitation of this study was that the frailty status of participants was based on just one assessment. Although the proportion of frail individuals in the study cohort was similar to that in the general population,[19] it seemed to limit our analyses of HbA_{1c} targets and change in frailty status in this subgroup (data not shown). It will, therefore, be interesting to study an elderly type 2 diabetes population with a higher proportion of frail patients in a clinical trial setting. More studies of this kind are needed to better understand individualised glycaemic targets and to lay the foundation for stronger treatment guidelines in elderly patients with type 2 diabetes.

In conclusion, our study reports the use of individualised targets in a clinical trial setting. Patients treated with vildagliptin were twice as likely to achieve their individualised treatment target (adjusted OR 3·16), accompanied by clinically relevant reductions in HbA_{1c}.

Panel: Research in context

Systematic review

We searched PubMed with English search terms including "elderly", "Type 2 Diabetes", "individualized", "treatment targets", and "treatment guidelines" for articles published between April, 2003, and April, 2013. We identified three guidelines suggesting individualisation of targets for glycaemic control in elderly patients with type 2 diabetes with limited life expectancy.[6,7,16] We found no evidence to support such an approach, which was emphasised in two of the guidelines.[6,16] Furthermore, we found no reports assessing the feasibility of individualised target setting in a clinical trial context.

Interpretation

This trial is a pragmatic study, in which we assessed the feasibility of setting and achieving investigator-defined individualised treatment targets for a period of 24 weeks in elderly patients with type 2 diabetes. Once set, a single oral agent, vildagliptin, was used to achieve the targets. Our results support the guidelines' recommendations[6,7,16] and show that individualised glycaemic target levels are achievable with vildagliptin without any tolerability issues in the growing elderly type 2 diabetes population.

Contributors

WDS represented the study investigators and participated in the study design, data collection, data review, initial data interpretation, and overall clinical interpretation. PMP played a crucial part in the study design, overall planning and implementation of the trial, data collection, initial data interpretation, and drafting of the manuscript. VL and WK contributed to study design and initial data interpretation. M-JH contributed to initial data interpretation. All authors were involved in manuscript revisions and are responsible for intellectual content.

Conflicts of interest

WDS has received research grants from Novartis and Novo-Nordisk, and speaker honoraria from Novartis, Novo-Nordisk, and Boehringer Ingelheim. WK, VL, M-JH, and PMP are employed by and own shares in Novartis.

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