Research: Treatment

Baseline characteristics in the VERIFY study: a randomized trial assessing the durability of glycaemic control with early vildagliptin-metformin combination in newly diagnosed Type 2 diabetes

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Abstract

Aim   To assess the long-term clinical benefits of early combination treatment with vildagliptin-metformin vs. standard-of-care, metformin monotherapy in the ongoing VERIFY study.

Methods   We randomized 2001 participants with multi-ethnic background, aged 18–70 years, having HbA_{1c} levels 48–58 mmol/mol (6.5–7.5%) and BMI 22–40 kg/m^2. Baseline data included HbA_{1c}, fasting plasma glucose and homeostasis model β-cell and insulin sensitivity. Standardized meal-tests, insulin secretion rate relative to glucose, and oral glucose insulin sensitivity were assessed in a subpopulation.

Results   Out of 4524 screened, data were collected from the 2001 eligible participants (53% women) across Europe (52.4%), Latin America (26.8%), Asia (17.2%), South Africa (3.1%) and Australia (0.5%). The median (interquartile range) disease duration was 3.4 (0.9, 10.2) months; mean (±SD) age 54.3±9.4 years; weight 85.5±17.5 kg and BMI 31.1±4.7 kg/m^2. Baseline HbA_{1c} was 52±3 mmol/mol (6.9±0.3%), fasting plasma glucose 7.5±1.5 mmol/l and the median (interquartile range) of fasting insulin was 109 (75–160) mU/l. Homeostasis model β-cell and insulin sensitivity values were 84% (60, 116) and 46% (31, 68), respectively. In those undertaking meal-tests, insulin secretion rate relative to glucose was 28±12 pmol/min/m^2/mmol/l and oral glucose insulin sensitivity was 353±57 ml/min/m^2.

Conclusions   Our current, multi-ethnic, newly diagnosed VERIFY population reflects a characteristic presence of early insulin resistance in participants with increased demand for insulin associated with obesity. The VERIFY study will provide unique evidence in characterizing therapeutic intervention in a diverse population with hyperglycaemia, focusing on durability of early glycaemic control.

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Introduction

There is debate about the optimum early pharmacological treatment of diabetes, although most authorities recommend metformin [1]. Beyond metformin it is usual to add a second therapy, but often this intensification occurs late, long after good glycaemic control is lost [2]. Second line agents include dipeptidyl peptidase-4 (DPP-4) inhibitors, which are good candidates for early combination therapy [1]. DPP-4 inhibitors improve glucose homeostasis synergistically with metformin even in mild hyperglycaemia, without the adverse effects of weight gain and hypoglycaemia [3,4].

VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of Type 2 diabetes) is an ongoing, 5-year, multinational, multi-ethnic study being conducted in 254 centres across 34 countries (Appendix: Table A1). We aimed to investigate, for the first time, the long-term benefits of early treatment intensification with a DPP-4 inhibitor (vildagliptin)-metformin combination over

What's new?

• The VERIFY study is the first study to assess the long-term clinical benefits of early combination treatment with a dipeptidyl peptidase-4 inhibitor (vildagliptin)-metformin vs. standard-of-care metformin monotherapy in people newly diagnosed with Type 2 diabetes.

• This report describes the baseline characteristics of a newly diagnosed population with Type 2 diabetes from a diverse geographical and ethnic background, demonstrating a classic profile of presence of early insulin resistance associated with elevated BMI as a surrogate for obesity.

• The study anticipates generating unique evidence on the progression of β-cell function, insulin resistance, early complications of diabetes, and effect on health status upon treatment with early vildagliptin-metformin combination.

standard-of-care metformin monotherapy in maintaining durable glycaemic control in people with newly diagnosed Type 2 diabetes.

In contrast to many cardiovascular outcome studies, we aimed to recruit a population reflecting the typical characteristics of newly diagnosed people living with diabetes worldwide.

Methods

Study design

The study design has been described in detail elsewhere [5]. Briefly, the VERIFY trial (NCT01528254) is an ongoing randomized, double-blind, parallel-group study consisting of a screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period during which the treatment is consecutively intensified, when clinically indicated at the investigators' discretion. Durability of glycaemic control, time to insulin initiation, changes in β-cell function and insulin sensitivity have been assessed over time.

The study protocol was approved by the Institutional Review Boards, Independent Ethics Committees and Competent Health Authorities in accordance with European Community Directive 2001/20/EC or as per national and international regulatory requirements in participating countries.

Study population

Participants aged 18–70 years, newly diagnosed with Type 2 diabetes (≤24 months) as per local diagnostic criteria, having centrally confirmed HbA$_{1c}$ levels between 48 mmol/mol (6.5%) and 58 mmol/mol (7.5%), and BMI 22–40 kg/m^2, were included in the study [5]. Individuals undergoing anti-diabetes treatment (except for short-term metformin) within

3 months prior to screening, or using any weight-loss medications were excluded, as were pregnant or breastfeeding women, and those with chronic liver disease or ongoing congestive heart failure [New York Heart Association (NYHA) III or IV].

Study assessments

Baseline measurements were obtained at the screening visit, or at the next visit prior to initiation of metformin up-titration. The primary efficacy assessments include HbA$_{1c}$ measurements to determine the time to initial treatment failure and the rate of loss in glycaemic control over time. Participants visit the study site every 13 weeks for 5 years to comply with the study procedures [5]. Laboratory samples are collected at each visit and analysed. Vital signs, electrocardiogram, body weight, haematology and biochemistry, fasting lipid profile and triglycerides, liver and renal function tests, urinalysis and adverse events are the key safety assessments. Major adverse cardiovascular events are independently adjudicated (exploratory endpoint) and an independent data safety committee monitors an unblinded periodic review of all safety data.
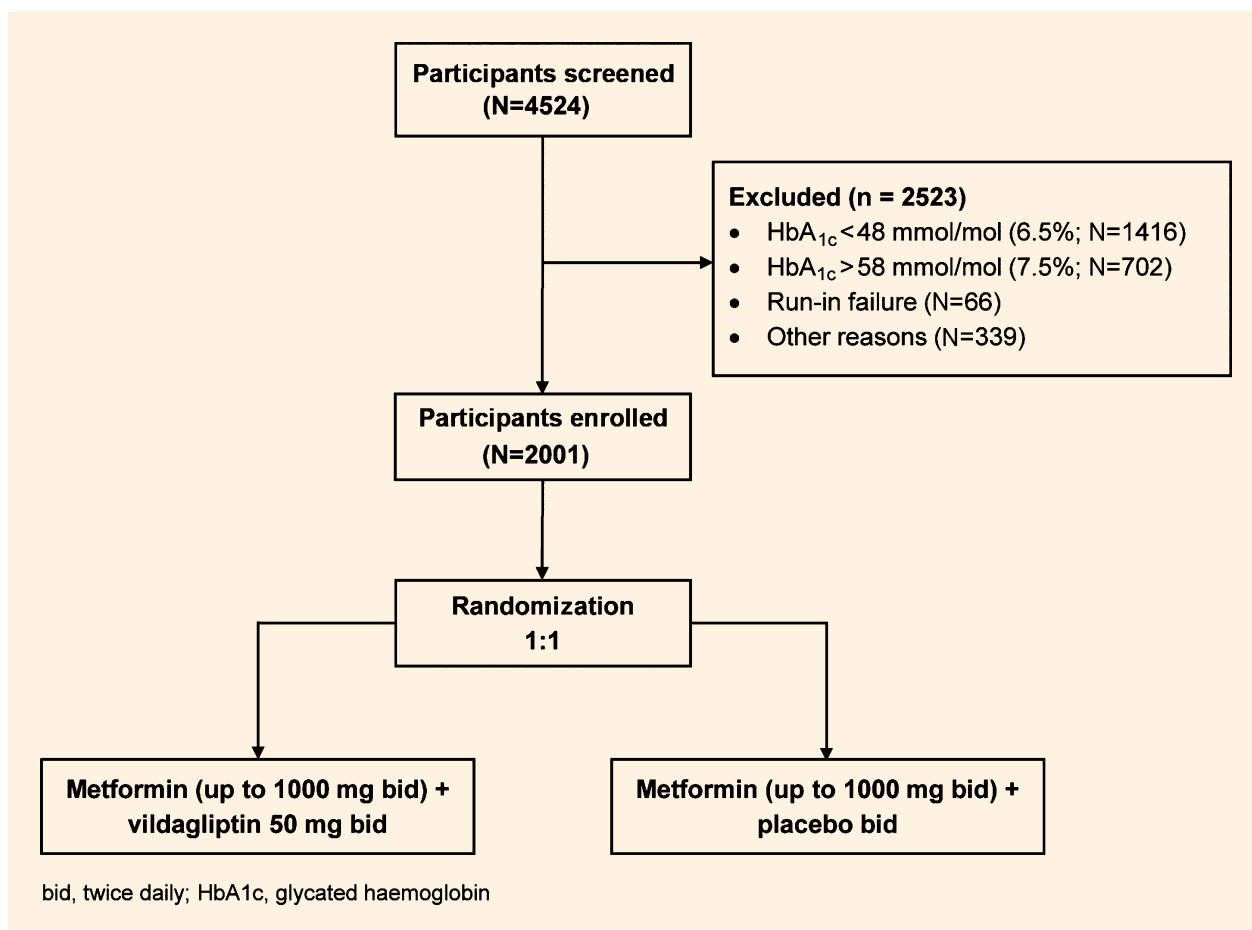
In a large subpopulation (n=462), standardized and locally adapted, annual meal-tests are performed for assessment of plasma glucose levels, insulin, and C-peptide concentrations. Indices of β-cell function (insulin secretion rate relative to glucose and homeostasis model assessment of β-cell function (HOMA-ß)), insulin sensitivity (oral glucose sensitivity index), and insulin resistance (HOMA-% sensitivity) are calculated [6,7].

Statistical analysis

Blinded baseline demographics and key glycaemic variables were analysed descriptively and summarized for all randomized participants. Categorical variables including age, gender and BMI were summarized with frequency and percentage, whereas continuous variables including duration of disease and HbA$_{1c}$ were summarized with mean ±SD.

Results

Recruitment of participants

Recruitment for the VERIFY trial started in March 2012 and randomization was completed in April 2014. A total of 2001 people, newly diagnosed with mild hyperglycaemia, were randomized out of the 4524 screened. The major reason for screening failure was an HbA$_{1c}$ value outside the protocol-defined, centrally assessed range of 48–58 mmol/mol (6.5–7.5%). A total of 66 participants were classified as run-in failures because of metformin-intolerance prior to up-titration to the lowest targeted dose of 1000 mg/day. Details of participants' dispositions are shown in Figure 1.

Participants screened
(N=4524)

Excluded (n = 2523)
- HbA$_{1c}$ < 48 mmol/mol (6.5%; N=1416)
- HbA$_{1c}$ > 58 mmol/mol (7.5%; N=702)
- Run-in failure (N=66)
- Other reasons (N=339)

Participants enrolled
(N=2001)

Randomization
1:1

Metformin (up to 1000 mg bid) + vildagliptin 50 mg bid

Metformin (up to 1000 mg bid) + placebo bid

bid, twice daily; HbA1c, glycated haemoglobin

FIGURE 1 Disposition of participants screened in the VERIFY trial

The geographical distribution of participants enrolled for this trial was: Europe (52.4%), Latin America (26.8%), Asia (17.2%), South Africa (3.1%) and Australia (0.5%).

Baseline characteristics

Overall demographics and baseline characteristics of participants are presented in Table 1.

The median (interquartile range) age of participants was 55 (48, 62) years, baseline HbA$_{1c}$ 52±3 mmol/mol (corresponding to 6.9±0.3%), fasting plasma glucose 7.5±1.5 mmol/l, and median (interquartile range) duration of diabetes 3.4 (0.9,10.2) months. Overall, men and women were often enrolled equally in the study despite some country-level differences. The mean baseline GFR was 87.4±18.5 ml/min/1.73m^2. Overall, 14.5% of the study population were smoking at baseline. Presence of early microvascular complications were reported in 8% of the participants enrolled.

At baseline the median (interquartile range) of fasting insulin was 109 (75–160) mU/l, and HOMA-ß and HOMA-% sensitivity values were 84% (60, 116) and 46% (31, 68), respectively. In the subset of participants (n=462) undertaking meal-tests, 2-hour plasma glucose values were 9.3±2.8 mmol/l,

insulin secretion rate relative to glucose was 28±12 pmol/min/m^2/mmol/l, and oral glucose sensitivity index value was 353±57 ml/min/m^2. Table 2 shows the variability of the meal-test measurements by geographic distribution.

Discussion

The VERIFY study cohort explores a newly diagnosed population with Type 2 diabetes with mild hyperglycaemia who have the potential for preservation of their β-cell function, and for achieving a long-term durable response to early therapy.

One principal goal of treating newly diagnosed drug-naive individuals is to achieve glycaemic control approaching normoglycaemia [8]. This trial explores the concept that optimization of therapy, in this case with an early vildagliptin-metformin combination, could overcome β-cell functional deterioration and thereby extend the durability of treatment over time.

Previous intervention studies on initial combination therapy have recruited participants with baseline HbA$_{1c}$ levels ≥64 mmol/mol (≥8.0%) [9–15]. Additionally, A Diabetes Outcome Progression Trial (ADOPT) [16] and Diabetes Prevention Program (DPP) [17] reported limited baseline variables with

Table 1 Demographics and baseline characteristics of participants

Variable	Total
Patient population, n	2001
Women, n (%)	1060 (53.0)
Age, years	
Median (IQR)	55 (48, 62)
Race, n (%)	
White European	1217 (60.8)
Black	49 (2.4)
Asian	373 (18.6)
Native American	210 (10.5)
Other	152 (7.6)
Duration of Type 2 diabetes, months	
Median (IQR)	3.4 (0.9, 10.3)
HbA$_{1c}$, mmol/mol (%)	52±3 (6.9±0.3)
FPG, mmol/l	7.5±1.5
Fasting insulin, median (IQR) (mU/L)	109 (75–160)
HOMA-%β, median (IQR) (%)	84 (60, 116)
HOMA-%sensitivity, median (IQR) (%)	46 (31, 68)
BMI, kg/m^2	31.1±4.7
Pulse rate, bpm	72.8±9.3
Systolic BP, mmHg	132.3±14.4
Diastolic BP, mmHg	80.6±8.6
HDL cholesterol, mmol/l	1.3±0.3
LDL cholesterol, mmol/l	2.9±0.9
Triglycerides, mmol/l	1.9±1.0
UALCRR, mg/mmol	
Median (Min–Max)	1.0 (0.1–262.3)
GFR (MDRD), mL/min/1.73m^2	87.4±18.5
History of diabetes and complications*, n (%)	
Proliferative retinopathy	1 (0.0)
Non-proliferative retinopathy	11 (0.5)
Nephropathy	26 (1.3)
Neuropathy	116 (5.8)
Foot ulcers	5 (0.2)
Metformin daily dose, mg	1597.3±396.5
Most common metformin dose; 2000 mg, n (%)	796 (39.8)

*Retinopathy and neuropathy were assessed according to the local protocols. BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA$_{1c}$, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-%β, homeostatic model assessment-%β; HOMA-%sensitivity, homeostatic model assessment-%sensitivity; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; SOC, system organ class; UALCRR, urinary micro albumin/creatinine ratio; ± indicates standard deviation (SD).

populations having a higher range of baseline HbA$_{1c}$. By contrast, the VERIFY trial will assess the durability of glycaemic response in individuals recruited at, or close to, diagnosis and with near-normal HbA$_{1c}$. The data show a 16.5% median decrease in β-cell function but marked reduction in insulin sensitivity to 46%. Insulin resistance is the reciprocal of the sensitivity, so those recruited have an insulin resistance that is double that found in people without diabetes.

Data obtained from the meal-test substudy are reflective of regional variations observed in plasma glucose, C-peptide, and insulin concentrations, which may prove important in the subgroup analysis of β-cell failure. Previously published data [18,19] demonstrated variations in postprandial glucose response, fasting insulin, and C-peptide concentrations between various ethnic groups. Such regional differences in the inter-relationships of early signs of increased insulin resistance (reduced sensitivity) and reduced β-cell function would be important to both document and interpret for optimized clinical decision making.

Long-term clinical trials normally pose a big challenge with low study participant retention. Evaluating the durability of treatment prospectively necessitates retention throughout the duration of the study. The VERIFY trial has an active retention programme, tailored to the needs of individuals, but over time the study is also carrying out innovative, relational real-time data monitoring to improve the retention rates.

The presence of baseline microvascular complications, including proliferative and non-proliferative retinopathy, nephropathy, neuropathy, and foot ulcer conditions, demonstrates the asymptomatic nature of Type 2 diabetes and early onset of foundation for its complications, emphasizing the importance of early treatment interventions to prevent or slow down the disease progression prior to advent of further diabetic complications.

The major strength of the VERIFY trial is the selection of a geographically distributed diverse, multi-ethnic population and long-term duration of 5 years for all the participants, ensuring the generalizability of the trial results and providing guidance in clinical decision making for the increasing number of people with newly diagnosed Type 2 diabetes. The enrolled participants display a classic profile of presence of early insulin resistance associated with elevated BMI as a surrogate for obesity. The study anticipates the generation of unique evidence for many geographical areas with limited or no prior epidemiological or other data on β-cell function, insulin resistance, early complications of diabetes, and effect on health status upon treatment with a DPP-4 inhibitor-metformin combination. The study is currently underway and will report in 2019.

Table 2 2-hour meal-test data by variables and geographical distribution

Variable	Europe	Latin America	Asia*	South Africa
Distribution, n (%)	267 (57.8)	152 (32.9)	32 (6.9)	11 (2.4)
Plasma glucose (mmol/l) Median (Min–Max)	9.3 (4.0–16.5)	7.9 (4.2–24.0)	10.4 (6.4–15.1)	9.8 (5.6–17.1)
Insulin (pmol/l) Median (Min–Max)	58.9 (3.5–286.6)	55.7 (7.6–404.5)	97.8 (20.7–435.6)	–
C-peptide (nmol/l) Median (Min–Max)	1.9 (0.4–5.7)	1.8 (0.3–4.8)	2.1 (0.5–5.0)	–

*values for Asia exclude India.

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Appendix

Table A1 Trial investigators and sites

Site number	Principal investigator	Institution
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31	Maria Lucheva	MHAT D-r Hristo Stambolski EOOD, Kazanlak, Bulgaria
32	Emilia Apostolova	MHAT Bratan Shukerov, Smolian, Bulgaria
33	Dotska Minkova	MHAT Razgrad, Razgrad, Bulgaria
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35	Tsvetodara Kuneva	DCC 1 Russe EOOD, Ruse, Bulgaria
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37	Hernan Yupanqui	DEXADIAB, Bogotá, Colombia
38	Arturo Orduz	Fundacion Hospital Infantil Universitario de San Jose, Bogota, Cundinamarca, Colombia
39	Fernando Manzur	Centro de Diagnostico Cardiológico, Cartagena, Bolivar, Colombia
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Table A1 (*Continued*)

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71	Joachim Sauter	Praxis Dr. Sauter, Wangen, Germany
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73	Joerg Simon	Praxis Dr. med. Joerg Simon, Fulda, Germany
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89	Michelle Wong	Shau Kei Wan Jockey Club GOPC, Hong Kong
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102	Rakesh Kumar Maliram Parikh	Diamed Clinical Research Services Pvt. Limited, Jaipur, Rajasthan, India
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Table A1 (*Continued*)

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Table A1 (*Continued*)

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200	Ruslan Sardinov	Institute of Experimental Medicine, St- Petersburg, Russia
201	Sergey Shustov	Military Medical Academy n.a.S.M Kirov, St-Petersburg, Russia
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