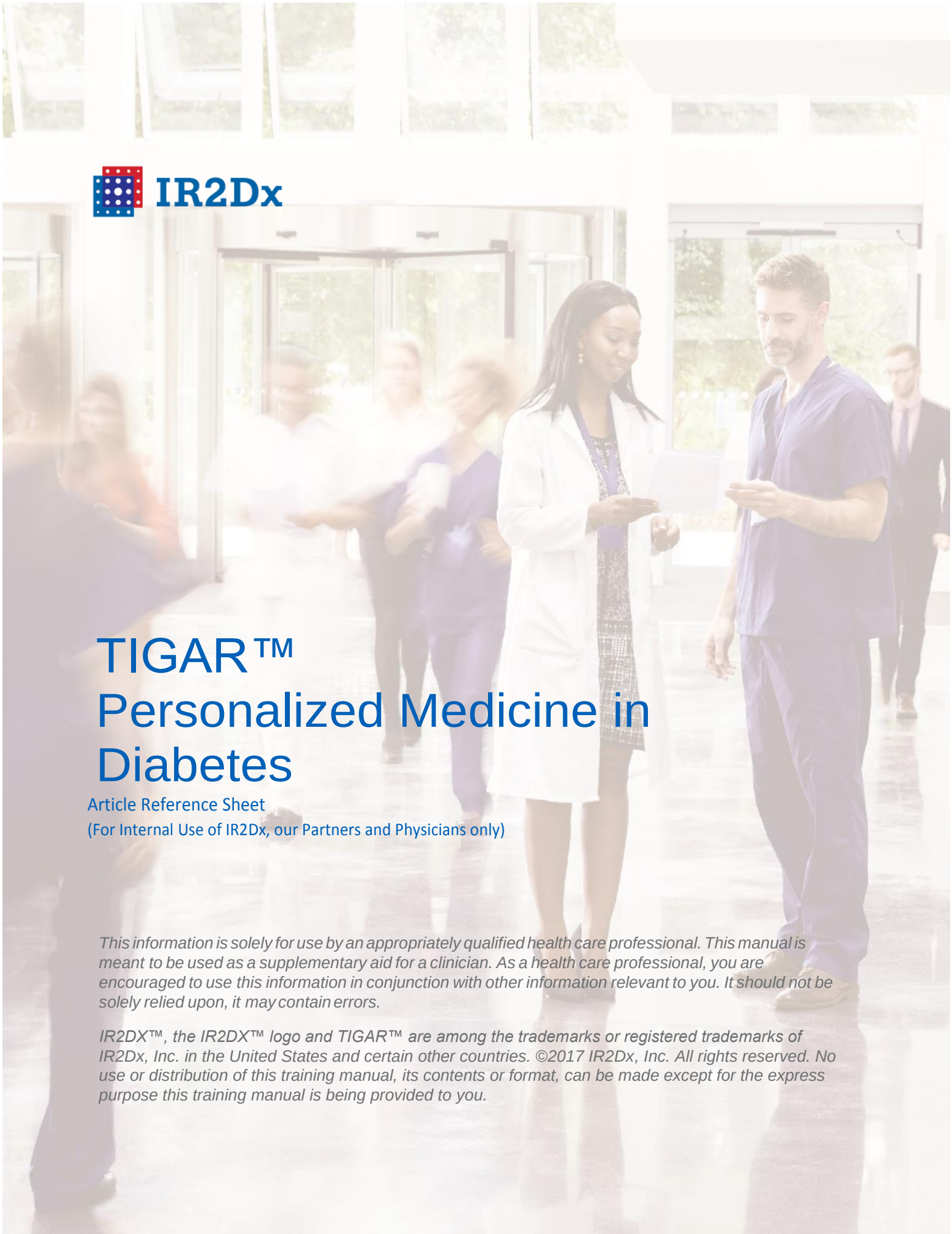

TIGAR™ Personalized Medicine in Diabetes

Article Reference Sheet

(For Internal Use of IR2Dx, our Partners and Physicians only)

This information is solely for use by an appropriately qualified health care professional. This manual is meant to be used as a supplementary aid for a clinician. As a health care professional, you are encouraged to use this information in conjunction with other information relevant to you. It should not be solely relied upon, it may contain errors.

IR2Dx Abstract Article Reference Sheet

(For Internal Use of IR2Dx, our Partners and Physicians Only)

These article abstracts are provided to clinicians for easy access to selected published articles broken into studies that were developed with people with diabetes and prediabetes. On our website, we have 42 articles with abstracts, including studies covering over 14,000 patients. (www.ir2dx.com)

DIABETES

(1) **Title of article:** Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin, Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. *Diabetes Obes Metab*. 2013 Jul; 15(7):642-9. Doi: 10.1111/dom.12076. Epub 2013 Feb 25.

Drug Classes compared in the study: Patients insufficiently controlled on metformin were randomized between two GLP-1 analogs to compare clinical markers in terms of beta-cell improvements and in post-meal glucose control.
IR2Dx TIGAR™ Markers used in the trial: C-peptide, insulin and HbA1c.

Abstract

AIM: Assess the pharmacodynamics of lixisenatide once daily (QD) versus liraglutide QD in type 2 diabetes insufficiently controlled on metformin.

METHODS: In this 28-day, randomized, open-label, parallel-group, multicentre study (NCT01175473), patients (mean HbA1c 7.3%) received subcutaneous lixisenatide QD (10 ug weeks 1 – 2, then 20 ug; n = 77) or liraglutide QD (0.6 mg week 1, 1.2 mg week 2, then 1.8 mg; n = 71) 30 min before breakfast. Primary endpoint was change in post prandial plasma glucose (PPG) exposure from baseline to day 28 during a breakfast test meal.

RESULTS: Lixisenatide reduced PPG significantly more than liraglutide [mean change in AUCO :30 – 4:30 h: −12.6 vs. −4.0 h mmol/L, respectively; $p < 0.0001$ (0:30 h = start of meal)]. Change in maximum PPG excursion was −3.9 mmol/l vs. −1.4 mmol/l,

respectively (p < 0.0001). More lixisenatide-treated patients achieved 2-h PPG <7.8 mmol/l (69% vs. 29%). Changes in fasting plasma glucose were greater with liraglutide (−0.3 vs. −1.3 mmol/l, p < 0.0001). Lixisenatide provided greater decreases in postprandial glucagon (p < 0.05), insulin (p < 0.0001) and C-peptide (p < 0.0001). Mean HbA1c decreased in both treatment groups (from 7.2% to 6.9% with lixisenatide vs. 7.4% to 6.9% with liraglutide) as did body weight (−1.6 kg vs. −2.4 kg, respectively). Overall incidence of adverse events was lower with lixisenatide (55%) versus liraglutide (65%), with no serious events or hypoglycaemia reported.

CONCLUSIONS: Once daily pre-breakfast lixisenatide provided a significantly greater reduction in PPG (AUC) during a morning test meal versus pre-breakfast liraglutide. Lixisenatide provided significant decreases in postprandial insulin, C-peptide (vs. an increase with liraglutide) and glucagon, and better gastrointestinal tolerability than liraglutide.

(2) **Title of article:** Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the Pioneer study. Pfützner A, Marx N, Lübben G, Langenfeld M, Walcher D, Konrad T, Forst T. *J Am Coll Cardiol.* 2005 Jan 21;45(12): 1925-31.

Drug Classes compared in the study: glimepiride, a sulfonylurea vs. pioglitazone, a thiazolidinedione (TZD).
IR2Dx TIGAR™ Markers used in the trial: HbA1c, adiponectin, insulin and hsCRP.

Abstract

OBJECTIVES: This study was performed to assess whether the anti-inflammatory and antiatherogenic effects of pioglitazone suggested by animal experiments are reproducible in man and independent from improvements in metabolic control.

BACKGROUND: Type 2 diabetes is associated with increased cardiovascular risk.

METHODS: A total of 192 patients were enrolled into a six-month, prospective, open-label, controlled clinical study. They were randomized to receive either pioglitazone (45 mg) or glimepiride (1 to 6 mg, with the intent to optimize therapy). Biochemical and clinical markers to assess therapeutic effects included HbA1c, fasting glucose, insulin, adiponectin, lipids, high- sensitivity C-reactive protein (hsCRP), intracellular adhesion molecule, vascular cell adhesion molecule, vascular endothelial growth factor,

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fibrinogen, von Willebrand factor, matrix metalloproteinase (MMP)-9, monocyte chemoattractant protein (MCP)-1, soluble CD40 ligand, and carotid intima-media thickness (IMT).

RESULTS: The study was completed by 173 patients (66 female, 107 male; age [+/- SD]: 63 +/- 8 years; disease duration: 7.2 +/- 7.2 years; HbA1c: 7.5 +/- 0.9%; pioglitazone arm: 89 patients). A comparable reduction in HbA1c was seen in both groups ($p < 0.001$). In the pioglitazone group, reductions were observed for glucose ($p<0.001$ vs. glimepiride group at end point), insulin ($p < 0.001$), low-density lipoprotein/high-density lipoprotein ratio ($p<0.001$), hsCRP ($p<0.05$), MMP-9 ($p<0.05$), MCP-1 ($p < 0.05$), and carotid IMT ($p < 0.001$), and an increase was seen in high-density lipoprotein ($p < 0.001$) and adiponectin ($p < 0.001$), Spearman ranks analysis revealed only one correlation between the reduction in cardiovascular risk parameters and the improvement in the metabolic parameters (MMP-9 and fasting blood glucose, $p<0.05$).

CONCLUSIONS: This prospective study gives evidence of an anti-inflammatory and antiatherogenic effect of pioglitazone versus glimepiride. This effect is independent from blood glucose control and may be attributed to peroxisome proliferator-activated receptor gamma activation.

(3) **Title of article:** Association of high-sensitivity C-reactive protein in advanced stage beta-cell dysfunction and insulin resistance in patients with type 2 diabetes mellitus. Pfützner A, Standl E, Strotmann HJ, Schulze J, Hohberg C, Lübben G, Pahler S, Schöndorf T, Forst T. *Clin Chem Lab Med.* 2006;44(5):556-60

Drug Classes compared in the study: Several such as diet (34.15%), metformin monotherapy (21.1%) and sulfonylurea monotherapy (17.0%).
IR2Dx TIGAR™ Markers used in the trial: HbA1c, hsCRP, intact proinsulin and insulin with a focus on hsCRP in this publication.

Abstract

BACKGROUND: Type 2 diabetes mellitus is associated with increased cardiovascular risk. One laboratory marker for cardiovascular risk assessment is high-sensitivity C-reactive protein (hsCRP).

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METHODS: This cross-sectional study attempted to analyze the association of hsCRP levels with insulin resistance, beta-cell dysfunction and macrovascular disease in 4270 non-insulin-treated patients with type 2 diabetes [2146 male, 2124 female; mean age +/-SD, 63.9+/-11.1 years; body mass index (BMI) 30.1+/-5.5 kg/m^2; disease duration 5.4+/-5.6 years; hemoglobin A1c (HbA1c) 6.8+/-1.3%]. It consisted of a single morning visit with collection of a fasting blood sample. Observational parameters included several clinical scores and laboratory biomarkers.

RESULTS: Stratification into cardiovascular risk groups according to hsCRP levels revealed that 934 patients had low risk (hsCRP <1 mg/L), 1369 patients had intermediate risk (hsCRP 1-3 mg/L), 1352 patients had high risk (hsCRP >3-10 mg/L), and 610 patients had unspecific hsCRP elevation (>10 mg/L). Increased hsCRP levels were associated with other indicators of diabetes-related cardiovascular risk (homeostatic model assessment, intact proinsulin, insulin, BMI, beta-cell dysfunction, all p<0.001), but showed no correlation with disease duration or glucose control. The majority of the patients were treated with diet (34.1%; hsCRP levels 2.85+/-2.39 mg/L) or metformin monotherapy (21.1%; 2.95+/-2.50 mg/L hsCRP). The highest hsCRP levels were observed in patients treated with sulfonylurea (17.0%; 3.00+/-2.43 mg/L).

CONCLUSIONS: Our results indicate that hsCRP may be used as a cardiovascular risk marker in patients with type 2 diabetes mellitus and should be evaluated in further prospective studies.

(4) **Title of article:** Effects of insulin glargine versus metformin on glycemic variability, microvascular and beta-cell function in early type 2 diabetes. Pistrosch F, Köhler C, Schaper F, Landgraf W, Forst T, Hanefeld M. *Acta Diabetol.* 2013 Feb 21. (Epub)

Drug Classes compared in the study: metformin and long acting insulin (insulin glargine).
IR2Dx TIGAR™ Markers used in the trial: intact proinsulin, C-peptide, insulin as part of HOMA and fasting plasma glucose in lieu of HbA1c.

Abstract

We investigated whether basal insulin as first- line treatment in recently diagnosed type 2 diabetes (T2D) can improve glucose control, microvascular function and preserve insulin secretion in comparison with metformin (MET). In this open-label, randomized,

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prospective 36-week study, 75 patients (44 m, 31 f, mean age 60.7 ± 9.2 year) were allocated to treatment with either MET 1,000 mg bid (*n* = 36) or insulin glargine (GLA) at bedtime (*n* = 39). At baseline and study end, we performed a continuous glucose monitoring for assessment of interstitial glucose (IG) and measured microvascular function using Laser-Doppler fluximetry. GLA versus MET treatment resulted in a more pronounced reduction in FPG (Δ: 3.1 ± 2.5 vs 1.4 ± 1.5 mmol/l; $p < 0.001$) and overall IG (Δ AUC. 671 ± 507 vs. 416 ± 537 mmol/l min; $p = 0.04$). Post-prandial PG and IG differences after a standardized test meal did not reach significance. Proinsulin/C-peptide and HOMA B as marker of endogenous insulin secretion were significantly more improved by GLA. Microvascular blood flow improved only in MET-treated patients. Early basal insulin treatment with GLA in T2D patients provided a better control of FPG, overall IG load and biomarker of beta-cell function compared to the standard treatment with MET. MET treatment resulted in an improvement of microvascular function. Studies of longer duration are needed to evaluate the durability of glucose control and β cell protection with early GLA treatment.

(5) **Title of article:** Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy: the PIOCOMB study. Hanefeld M, Pfützner A, Forst T, Kleine I, Fuchs W. *Cardiovascular Diabetol.* 2011, Jul 14; 10:65.

Drug Classes compared in the study: pioglitazone, metformin and insulin (basal insulin).
IR2Dx TIGAR™ Markers used in the trial: HbA1c, adiponectin and hsCRP.

Abstract

BACKGROUND: We analyzed specific effects of an add-on therapy with pioglitazone compared to metformin and their combination in patients with basal insulin treatment on biomarkers of CV risk.

METHODS: In this double-blind, randomized, multicentre, active comparator controlled trial, 121 patients with type 2 diabetes were enrolled. Inclusions: treatment with basal insulin, HbA_{1c} 6.5%-8.5%, age 30-75 years. After glargine therapy over 2 weeks for titration towards FBG ≤ 7.8 mmol/L, patients received either (A) bid 850 mg metformin (n = 42), (B) bid 15 mg pioglitazone (n = 40), or (C) 30 mg pioglitazone plus 1.7 g

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metformin (n = 39) over 6 months. Matrix Metal Proteinase 9 (MMP-9) was primary objective, together with biomarkers of CV risk.

RESULTS: Pioglitazone (B) reduced MMP-9 versus baseline by 54.1± 187.1 ng/mL, with metformin (A) it was increased by 49.6 ±.336.2 ng/mL (p = 0.0345; B vs. A), and with the combination of both (C) it was decreased by 67.8 ± 231.4 ng/mL (A vs. C: p = 0.0416; B vs. C: p = 0.8695). After logarithmic transformation due to high variances the exploratory results showed significance for A vs. B (p = 0.0043) and for A vs. C (p = 0.0289).

Insulin dosage was reduced by 7.3 units in group B (p < 0.0001), by 6.0 units in C (p = 0.0004), but was increased by 2.5 units (p = 0.1539) in A at follow up. Reduction in hsCRP was significant within treatment groups for B (p = 0.0098) and C (p < 0.0001), and between the groups for A vs. C (p = 0.0124). All three single regimens reduced PAI-1. Adiponectin was significantly elevated in B and C (p < 0.0001) and between-groups. HbA_{1c} was only significantly decreased in the combination group. No significant effects were observed for NFkB and PGFα peripheral edema was seen in 11.9% vs 40.0% vs 20.5%, and weight change was -0.7 kg vs +4.3 kg vs +2.7 kg (A vs B vs C).

CONCLUSIONS: Addition of pioglitazone but not of metformin reduces MMP-9, hsCRP and increased insulin sensitivity and adiponectin in this study. The combination of both had no additional effect on inflammation. Pioglitazone is suggested to be a rational add-on therapy to basal insulin in patients with high CV risk.

(6) **Title of article:** Successful switch from insulin therapy to treatment with pioglitazone in type 2 diabetes patients with residual beta-cell function: results from the PIOSwitch study. Hohberg C, Pfützner A, Forst T, T Lübben G, Karagiannis E, Borchert M, Schöndorf T. *Diabetes Obes Metab.* 2009 May; 11(5):464-71.

Drug Classes compared in the study: switch from insulin to combination of pioglitazone and glimepiride.
IR2Dx TIGAR™ Markers used in the trial: HbA1c, adiponectin, C-peptide, insulin, intact proinsulin & hsCRP.

Abstract

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AIM: Insulin treatment is considered to be the final option for patients with progressive type 2 diabetes. This study investigated, whether reconverting type 2 patients from insulin treatment to oral treatment using pioglitazone is possible without deterioration of blood glucose control.

METHODS: The PioSwitch study was a prospective, open label, proof of concept study. Thiazolidinedione-naïve patients with residual beta-cell function were switched from an existing insulin therapy to treatment with pioglitazone and glimepiride for 6 months. Efficacy was assessed by laboratory parameters and scores for evaluation of metabolic control, beta-cell function, insulin resistance and cardiovascular risk.

Results: In total, 98 patients [66 men, 32 women, age (mean+/- s.d.): 59 ± 9 years; disease duration: 5.6 ±3.6 years; Hemoglobin A1c. (HbA1c): 6.9 ±0.8%; body mass index (BMI): 33.9 ±5.2 kg/m^2, initial daily insulin therapy dose: 0.36 ± 0.3 U/kg body weight] out of 117 screened patients were treated. During the observation period, 23 patients were prematurely terminated because of an increase in HbA1c from baseline > 0.5% or for other reasons. In 75 patients (76%), no deterioration of glucose metabolism occurred and additional improvements were seen in the majority of the observation parameters [baseline vs. endpoint; HbA1c: 6.79 ± 10.74%/6.66 ± 0.69% ($p < 0.05$), glucose: 6.4 ± 1.5/5.2 ± 1.4 mmol/l $p < 0.001$), adiponectin: 7 ± 3 mg/l/17 ± 8 mg/l $p < 0.001$), C-peptide: 987 ± 493/1756 ± 789 pmol/l ($p < 0.001$), sensitivity index derived from the intravenous glucose tolerance test (SI(ivGTT): 1.21 ±0.85/1.49 ± 0.95 ($p < 0.05$), hsCRP 3.3: ± 2.4/2.6 ± 2.4 mg/l ($p < 0.01$), macrophage chemo attractant protein)MCP1): 487 ± 246/382 ± 295 ng/l ($p < 0.05$)]. BMI increased from 33.8 ± 5.1 to 34.4 ± 5.3 kg/m^2 ($p < 0.001$).

Conclusions: The switch from insulin therapy resulting in a moderately HBA1c level, to oral treatment with pioglitazone was successful in a majority of patients with sufficient residual beta-cell function. It also allows a simple and less expensive therapy with a better cardiovascular risk marker profile.

(7) **Title of article:** Pioglitazone in addition to metformin improves erythrocyte deformability in patients with type 2 diabetes mellitus. Forst T, Weber MM, Löbig M, Lehmann U, Müller J, Hohberg C, Friedrich C, Fuchs W, Pfützner A. *Clin Sci (Lond).* 2010 July 9; 119(8): 345-51.

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Drug Classes compared in the study: metformin, pioglitazone and glimepiride.
IR2Dx TIGAR™ Markers used in the trial: HbA1c, fasting insulin, intact proinsulin and adiponectin.

Abstract

Aim: The aim of the present study was to compare the effect of PIO (pioglitazone) or GLIM (glimepiride) on erythrocyte deformability in T2DM (Type 2 diabetes mellitus).

Methods: The study covered 23 metformin-treated T2DM patients with an HbA1c (glycated haemoglobin) > 6.5%. Patients were randomized to receive either PIO (15 mg, twice a day) or GLIM (1mg, twice a day) in combination with metformin (850 mg, twice a day) for 6 months. Blood samples were taken for the measurement of fasting glucose, HbA1c, fasting insulin, intact proinsulin, adiponectin and Hct (haematocrit). In addition, the erythrocyte El (elongation index) was measured using laser diffractoscopy.

Results: Both treatments significantly improved HbA1c levels (PIO, -0.9+/-1.1%; GLIM, -0.6+/-0.4%; both P<0.05) and resulted in comparable HbA1c levels after 6 months (PIO, 6.5+/-1.2%; GLIM, 6.2+/-0.4%). Treatment with PIO reduced fasting insulin levels (-8.7+/-15.8 milli-units/l; P=0.098), intact proinsulin levels (-11.8+/-9.5 pmol/1; P<0.05} and Hct (-1.3+/-2.3%; P=0.09), whereas adiponectin levels increased (8.2+/-4.9 microg/ml; P<0.05). No significant change in these parameters was observed during GLIM treatment. PIO improved the El, resulting in a significant increase in El at all physiological shear stress ranges (0.6-6.0 Pa; P<0.05). The improvement in El correlated with the increase in adiponectin levels (r-0.74; P<0.001), and inversely with intact proinsulin levels (r=-0.47; P<0.05).

Conclusions: This is the first study showing an improvement in El during treatment with PIO, which was associated with an increase in adiponectin and a decrease in intact proinsulin levels, but independent of glycaemic control.

(8) **Title of article:** The switch from sulfonylurea to preprandial short-acting insulin analog substitution has an immediate and comprehensive beta-cell protective effect in patients with type 2 diabetes mellitus. Pfützner A, Lorra B, Abdollahnia MR, Kann PH, Mathieu D, Pehnert C, Oligschleger C, Kaiser M and Forst T. *Diabetes Technol Ther.* 2006 Jun; 8(3):375-84.

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Drug Classes compared in the study: glimepiride at baseline followed by substituting short acting insulin.
IR2Dx TIGAR™ Markers used in the trial: glucose in lieu of HbA1c, insulin, C-peptide, intact proinsulin and adiponectin.

Abstract

BACKGROUND: Supplementary insulin therapy provides assistance to meal-time insulin secretion in patients with type 2 diabetes and may have protective effects on beta-cell function.

METHODS: This study explored the immediate effect of supplementary insulin therapy on beta-cell function in patients with glimepiride monotherapy (five women, 15 men; 61.8 +/- 6.4 years old; body mass index, 31.1 +/- 4.4 kg/m (2); hemoglobin A 1c, 7.0 +/- 1.3%). After 1 week of continued glimepiride therapy, the patients were randomized either to continue with their oral treatment or to switch to a fixed-dose supplementary insulin therapy (8 U of insulin aspart subcutaneously before each meal) for another week. Oral glucose tolerance tests (OGTTs) after drug uptake were performed at days 7 and 14, with measurement of glucose, insulin, C-peptide, intact and total proinsulin, glucagon, lactate, free fatty acids, and adiponectin.

RESULTS: Significant reductions from baseline were seen in the supplementary insulin therapy group for the fasting values of insulin (from 13.1 +/- 5.1 microU/mL to 10.6 +/- 5.2 microU/mL, P < 0.01), intact proinsulin (from 18.3 +/- 11.2 pmol/L to 10.3 +/- 4.6 pmol/L, P micro 0.05), total proinsulin (from 43.3 +/-22.7 pmol/L to 29.7 +/- 14.5 pmol/L, P < 0.01), split proinsulin (from 24.9 +/-13.8 pmol/L to 19.4 +/- 10.8 pmol/L, P micro 0.01), and the degree of beta-cell dysfunction (P < 0.05). Also, lower values for intact and total proinsulin and split proinsulin in the OGTT were observed in this group during the OGTT at the endpoint, while no changes at all occurred in the glimepiride group.

CONCLUSIONS: A fixed low-dose preprandial insulin aspart therapy resulted in an overall beta-cell protection with an improved fasting beta-cell secretion profile already within 1 week. Our study indicates that supplementary insulin therapy might be a reasonable alternative to bedtime basal insulin injections for initiation of insulin therapy in patients with type 2 diabetes.

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(9) **Title of article:** IRIS-II study: intact proinsulin is confirmed as a highly specific indicator for insulin resistance in a large cross-sectional study design. Pfützner A, Standl E, Hohberg C, Konrad T, Stratmann HJ, Lübben G, Langenfeld MR, Schulze J, Forst T. *Diabetes Tech.* 2005 Jun; 7(3):478-86

Drug Classes compared in the study: sulfonylureas (726 patients) metformin (908), sulfonylurea and metformin (534) metformin and glinide (105) metformin and glitazones (131) and various other anti-diabetic medications or no treatment.
IR2Dx TIGAR™ Markers used in the trial: HbA1c, insulin, intact proinsulin.

Abstract

BACKGROUND: The cross-sectional IRIS-II study tried to assess the prevalence of insulin resistance and macrovascular disease in orally treated patients with Type 2 diabetes.

METHODS: In total, 4,270 patients were enrolled into the study (2,146 male, 2,124 females; mean +/-SD age 63.9 +/- 11.1 years; body mass index 30.1 +/- 5.5 kg/m^2; duration of disease 5.4 +/- 5.6 years; hemoglobin A1c 6.8 +/- 1.3%). The study consisted of a single morning visit with completion of a standardized questionnaire and collection of a fasting blood sample.

RESULTS: The mean intact proinsulin value was 11.4 +/- 12.4 pmol/L (normal range < 10 pmol/L). Homeostasis model assessment resulted in 1,147 insulin-sensitive patients (26.9%) and 3,123 patients (73.1%) with insulin resistance. Of the latter patients 1,465 (34.3% of all patients) had also elevated intact proinsulin values, while 1,658 (38.8%) had no proinsulin elevation. In contrast, 1,042 (24.4%) of the insulin-sensitive patients had normal intact proinsulin, and only 105 (2.4%) had elevated intact proinsulin concentrations (chi2 test P < 0.0001). A specificity of 93.2% (sensitivity 46.9%) was calculated for elevated intact proinsulin as an indirect marker for insulin resistance. Of the 1,451 patients treated with sulfonylurea 52% had elevated intact proinsulin values and increased prevalence of cardiovascular complications (odds ratio 1.45).

CONCLUSION: Type 2 patients with elevated fasting intact proinsulin values can be regarded as being insulin resistant. The results confirm that fasting intact proinsulin is a suitable measure for beta-cell dysfunction and insulin resistance in type 2 diabetes and may be used to support therapeutic decisions.

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(10) **Title of article:** Cardiovascular Benefits of GLP-1-Based Therapies in Patients with Diabetes Mellitus Type 2: Effects on Endothelial and Vascular Dysfunction beyond Glycemic Control. Forst T, Weber M, and Pfutzner A. *Exper Diab Research* 2012, Apr. 17.doi: 10.1155/2012/635472

Drug Classes compared in the study: Review article on the role of GLP1 and DPP-4 inhibitors in the management of type 2 diabetes beyond glycemic control
IR2Dx TIGAR™ Markers used in the trial: Discusses insulin, intact proinsulin and C-peptide and adiponectin, as well as other important cardiovascular markers like PAI-1.

Abstract

Type 2 diabetes mellitus (T2DM) is a progressive multisytemic disease accompanied by vascular dysfunction and a tremendous increase in cardiovascular mortality. Numerous adipose-tissue-derived factors and beta cell dysfunction contribute to the increased cardiovascular risk in patients with T2DM. Nowadays, numerous pharmacological interventions are available to lower blood glucose levels in patients with type 2 diabetes. Beside more or less comparable glucose-lowering efficacy, some of them have shown limited or probably unfavorable effects on the cardiovascular system and overall mortality. Recently, incretin-based therapies (GLP-1 receptor agonists and DPP-IV inhibitors) have been introduced in the treatment of T2DM. Besides the effects of GLP-1 on insulin secretion, and gastrointestinal motility, recent studies suggest a couple of direct GLP-1 effects on endothelial and vascular function and potential consequences on the cardiovascular outcome in patients with T2DM treated with GLP-1 receptor agonists or DPP-IV inhibitors.

(11) Title of Article: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Inzucchi SE et. A. for the EMPA-REG Outcome Investigators. *N Engl J Med* 2015; 372-:2117-2128 Nov. 26, 2015.

Drug Classes compared in the study: Major long term cardiovascular outcome trial comparing placebo against empagliflozin, a SGLT-2 inhibitor. Patients were existing diabetes patients with an elevated HbA1c were already numerous other medications, such as short acting insulins, long acting insulins, metformin, sulfonylureas, TZD;'s, DPP-4 inhibitors and GLP-1 analogs. At the end of the study, the patient's drug mix changed in both the placebo and drug study arm.

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IR2Dx TIGAR™ Markers used in the trial: The only biomarkers specifically mentioned in the study were a glucose marker, HbA1c and eGFR, the latter being used to assess degree of renal impairment at the beginning and end of the study. Other cardiovascular risk markers were reviewed, such as cholesterol, but, surprisingly, not hsCRP. This study is included because of the importance of the study findings, which are elucidated below. This drug from the SGLT-2 class is the first in the class to demonstrate dramatic reductions in the risk of cardiovascular events and at a hazard ratio nearly 10% below anything seen previously with pioglitazone, rosiglitazone or liraglutide, TZD's and GLP-1 analog, respectively. The other two approved and a third before regulators are performing their own cardiovascular safety studies with results expected in 2017 to 2019.

Abstract

Background: The effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity in patients with type 2 diabetes at high cardiovascular risk are not known.

Methods: We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

Results: A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to .99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

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Conclusions: Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.

Important update on SGLT-2 inhibitors in clinical practice and from just published clinical trial involving real-world study across six countries, including US. U.K., Germany, Sweden, Norway and Denmark involving 364,828 patients. The pooled results were presented at the American College of Cardiology Meeting in Washington D.C. on March 19, 2017. The research was presented by Mikhail Kosiborod, MD, FACC at the ACC meeting. For the primary endpoint of Hospitalization for heart failure (HHF) there was a reduction that favored the three approved SGLT-2 inhibitors over other treatments in each of the six countries. In total, there were 961 HHF during the study period, and the incidence was lower with the SGLT-2 inhibitors (hazard ratio 0.61; p < 0.001). The SGLT-2 treated patients also saw a lower incidence of the secondary endpoint of all-cause death in each country and the total number was 1.334 (HR, 0.49; p < 0.001).

(12) **Title of Article**: Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators**N Engl J Med* 2016; 375:311-322July 28, 2016DOI: 10.1056/NEJMoa1603827

Drug Classes compared in the study: Major long term cardiovascular outcome trial comparing subcutaneous injections of placebo vs. liraglutide, a GLP-1 receptor agonist. Patients were existing diabetes patients with an elevated HbA1c were already numerous other medications, such as short acting insulins, long acting insulins, metformin, sulfonylureas, TZD;'s acarbose and SGLT-2 inhibitors. DPP-4 inhibitors and GLP-1 analogs were not allowed in the last three months before enrollment. i. At the end of the study, the patient's drug mix changed in both the placebo and drug study arm, including the addition of DPP-4 inhibitors.

IR2Dx TIGAR™ Markers used in the trial: The only biomarkers specifically mentioned in the study were a glucose marker, HbA1c and eGFR, the latter being used to assess degree of renal impairment at the beginning and end of the study. This study is included because of the

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importance of the study findings, which are elucidated below. It is interesting in that four or our TIGAR markers were used as key laboratory markers in their other major study liraglutide 3.0 mg dose in obese no-diabetic patients.

Abstract

BACKGROUND: The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS: In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS: A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS: In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)

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(13) **Title of Article**: Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group**N Engl J Med* 2015; 373:232-242July 16, 2015DOI: 10.1056/NEJMoa1501352

Drug Classes compared in the study: This study was a long-term cardiovascular outcome trial comparing two doses of sitagliptin vs. a placebo and included many other antidiabetic agents as required for the patient to reach target HbA1c levels.**IR2Dx TIGAR™ Markers used in the trial:** Each institution had flexibility as to what additional biomarkers that were used to assess patient response to antidiabetic treatments. As such, only eGFR and HbA1c were consistently and routinely evaluated in this study. This study is included because sitagliptin is by far the most widely used DPP-4 inhibitor and because it was the first in this class to demonstrate no increased risk of cardiovascular events compared to placebo.

Abstract

BACKGROUND: Data are lacking on the long-term effect on cardiovascular events of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease.

METHODS: In this randomized, double-blind study, we assigned 14,671 patients to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, aimed at reaching individually appropriate glycemic targets in all patients. To determine whether sitagliptin was noninferior to placebo, we used a relative risk of 1.3 as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

RESULTS: During a median follow-up of 3.0 years, there was a small difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, −0.29 percentage points; 95% confidence interval [CI], −0.32 to −0.27). Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular

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outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98). There were no significant between-group differences in rates of acute pancreatitis (P=0.07) or pancreatic cancer (P=0.32).

CONCLUSIONS: Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events. (Funded by Merck Sharp & Dohme; TECOS ClinicalTrials.gov number, NCT00790205.

(14) **Title of Article**: Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from PROspective, pioglitazone Clinical Trial In macro Vascular Events (PROactive 10). Wilcox, R, Kupfer S, Erdmann E. on behalf of the PROactive Study investigators, A*HJ*; April 2008 Vol 155, Issue 4, 712-717.

Drug Classes compared in the study: multiple in standard of care plus pioglitazone vs. placebo comparative arms
IR2Dx TIGAR™ Markers used in the trial: HbA1c. This study is included because pioglitazone is the first drug to undertake a successful cardiovascular clinical outcome study in a high-risk population of patients. The TIGAR biomarkers have been studied extensively with pioglitazone and other TZD's and have consistently demonstrated correlation with positive changes in glucose levels and cardiovascular risk.

Abstract

BACKGROUND: Composite end points of major adverse cardiovascular events (MACEs) are standard measures for comparing treatment in large cardiovascular outcome studies. This analysis from PROspective, pioglitazone Clinical Trial In macro Vascular Events (PROactive) evaluated the effects of pioglitazone on the prespecified MACE end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (MACE1) and on 6 post hoc MACE composites (various combinations of all-cause, cardiovascular, or cardiac mortality; plus, nonfatal myocardial infarction; plus nonfatal stroke; and/or acute coronary syndrome) in patients with type 2 diabetes.

METHODS: PROactive was cardiovascular outcome study that randomized patients with type 2 diabetes to pioglitazone (n=2605) or placebo (n=2633), in addition to existing glucose-lowering and cardiovascular medications. Pioglitazone was titrated from 15 to 45 mg/d based on tolerability. Mean follow-up was 34.5 months.

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RESULTS: At final visit, 257 (9.9%) pioglitazone-treated and 313 placebo-treated patients had a first event that contributed to the MACE 1 end point (hazard ratio 0.82, 95% CI 0.70-97, P= .0201). There were statistically significant differences in favor of pioglitazone in 5 of the other MACE end points (P < .05) and a trend to benefit in the sixth (P = .052), with hazard ratios of 0.79 to 0.83.

CONCLUSIONS: In patients with advanced type 2 diabetes at high risk for cardiovascular events, pioglitazone treatment resulted in significant risk reductions in MACE composite end points to 3 years.

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PREDIABETES

(1)	**Title of article:** Effect of pioglitazone and ramipril on Biomarkers of Low-Grade Inflammation and Vascular Function in Nondiabetic Patients with Increased Cardiovascular Risk and an Activated Inflammation: Results from the PIOace Study. Pfützner A, Hanefeld M, Dekordi LA, Müller J, Kleine I, Fuchs W and Forst T. *J. Diabetes Sci Technol* 2011 Jul 1;5(4):989-98.

Drug Classes compared in the study: ramipril for hypertension and pioglitazone as study drug or the combination in hypertensive non-diabetic patients with cardiovascular risks.

IR2Dx TIGAR™ Markers used in the trial: HbA1c, hsCRP, adiponectin, intact proinsulin and insulin.

Abstract

AIMS: This study investigated the effects of pioglitazone (PIO), ramipril (RAM), or their combination (PIRA) on low-grade inflammation in nondiabetic hypertensive patients with increased cardiovascular risk.

METHODS AND. RESULTS: Patients enrolled in this placebo-controlled, double-blind, randomized, parallel trial (72 males, 77 females, aged 60 ± 9 years, body mass index 30.4 ± 4.7.kg/m^2, duration of hypertension 9 ± 8 years) were treated with either 30/45mg PIO (dose titration), 2.5/5 mg RAM, or their combination for 12 weeks. A reduction in high-sensitivity C-reactive protein was observed with PIO (-0.89 ± 1.98 mg/liter; -25%) and PIRA (-0.49 ± 2.11 mg/liter; -16%), while an increase was seen with RAM (0.58 ± 2.13 mg/liter; +20%, $p < .05$ vs PIO and PIRA). The 24-hour blood pressure profile showed a small increase with both monotherapies but a decrease with PIRA ($p < .05$ vs PIO). Improvements in biomarkers of chronic systemic inflammation and insulin resistance (IR) were observed in the PIO and PIRA arms only [PIO/RAM/PIRA:
homeostasis model of assessment of IR: -0.78 ± 1.39 (-29%)/0.15 ± 1.03 (+5%)/-1.44 ± 2.83 (-40%);
adiponectin: 8.51 ± 5.91 (+104%)/ 0.09 ± 2.63 (+1%)/8.86 ± 6.37 mg/liter (+107%);
matrix metallo-proteinase-9: -48 ± 127 (-12%)/-1 ± 224 (0%)/-60 ± 210 ng/ml (-13%), $p < .05$ for RAM vs PIO or PIRA in all cases.

CONCLUSIONS: Our 3-month study in nondiabetic hypertensive patients showed a decrease in biomarkers of IR and chronic systemic inflammation with the PIO

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monotherapy and the PIRA combination only, which may help to explain some findings in other cardiovascular outcome trials.

(2) **Title of article:** Changes in insulin resistance and cardiovascular risk induced by PPARgamma activation have no impact on RBP4 plasma concentrations in nondiabetic patients. Pfützner A, Schöndorf T, Hanefeld M, Lübben G, Kann PH, Karagiannis E, Wilhelm B, Forst T. *Horm Metab Res* 2009 Mar;41(3):202-6.

Drug Classes compared in the study: non-diabetic patients randomized to either simvastatin, pioglitazone or the combination.
IR2Dx TIGAR™ Markers used in the trial: hsCRP, insulin and adiponectin.

Abstract

Retinol binding protein 4 (RBP4) has recently been suggested as a good biomarker for insulin resistance and the metabolic syndrome. With this study, we wanted to investigate the effect of pioglitazone (PIO) and simvastatin (SIMVA) on insulin resistance and RBP4 plasma concentrations in nondiabetic patients with metabolic syndrome and increased risk for cardiovascular complications. The prospective, parallel, randomized, double-blind clinical trial was performed with 125 nondiabetic patients with increased cardiovascular risk (78 females, 47 males, age (mean+/-STD): 58.6+/-7.8 years, BMI: 30.8+/-4.2 kg/m (2)). They were randomized to either receive PIO (45 mg) + placebo, SIMVA (40 mg) + placebo, or PIO + SIMVA for 3 months. Key outcome measures were the HOMA (IR)-Score, an oral glucose tolerance test, adiponectin, hsCRP, and RBP4 at baseline and endpoint. No correlation could be detected between the HOMA (IR) values or the impaired fasting glucose tolerance status and RBP-4. Treatment with PIO alone or in combination with SIMVA resulted in a significant improvement of the HOMA (IR)-Score and the adiponectin values, while no change in HOMA (IR) and a decrease in adiponectin ($p<0.05$) were observed with SIMVA monotherapy. Reductions of hsCRP were seen in all three treatment arms ($p<0.001$). No changes of the plasma RBP4 concentrations were observed in any of the treatment groups (PIO: 35.6+/-7.2/36.3+/-8.7 ng/ml, PIO+SIMVA: 36.5+/-10.8/36.5+/-8 ng/ml, SIMVA: 36.1+/-8.1/36.6+/-11.1 ng/ml, all n.s. vs. baseline). Despite a partial or comprehensive improvement in insulin resistance and/or cardiovascular risk indicators in all treatment arms, no change in RBP4-levels could be observed. The regulation of RBP4 expression and secretion occurs through biochemical pathways independent from those influenced by pioglitazone or simvastatin.

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(3) **Title of article:** Increased prevalence of cardiovascular disease and risk biomarkers in patients with unknown type 2 diabetes visiting cardiology specialists; results from the DIASPORA study. Schöndorf T, Lübben G, Karagiannis E, Erdmann E, Forst T, Pfützner A. *Diab Vasc Dis Res* 2010 Apr 7(2): 145-50 EPUB 2010 Feb 18.

Drug Classes compared in the study: various medications for diabetes, hypertension and hypocholesteremia.
IR2Dx TIGAR™ Markers used in the trial: HbA1c, hsCRP, insulin and intact proinsulin.

Abstract

BACKGROUND: Patients with diabetes mellitus and IGT have a high risk for cardiovascular events. It is tempting to speculate that these patients are often first seen by cardiologists.

DESIGN: This cross-sectional study investigates the diabetes prevalence in cardiology care units and the correlated metabolic conditions as assessed by several circulating biomarkers.

METHODS: Patients aged 55 or older with suspected or overt coronary heart disease were eligible for trial participation. Fasting blood samples were drawn from patients to determine HOMA score, glycaemic and lipid profile, and several risk biomarkers. An OGTT was performed in patients without known diabetes.

RESULTS: We enrolled 530 patients (181 males, 349 females, mean age, 68+/-7 years) in this study from 22 German cardiology centres; 156 patients (29.4%) had known diabetes and OGTT revealed that 184 patients (34.7%) had no diabetes, 106 patients (20.0%) had IGT or IFG and 84 patients (15.9%) were newly diagnosed with diabetes. Increased cardiovascular risk as reflected by increased hsCRP, ICAM and MMP-9 values was observed in diabetes patients. A higher cardiovascular biomarkers risk profile was seen in the IGT/IFG cohort.

CONCLUSIONS: This study confirms the observation that one third of patients of a cardiologic care unit suffer from impaired glucose regulation. Furthermore, the cardiology patients with previously unknown glucose homeostasis abnormalities had a higher prevalence of macrovascular disease and an impaired biomarker risk profile. This study underlines the importance of joint treatment efforts by cardiologists in concert with diabetologists for treatment of this patient group at high risk for cardiovascular events.

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(4)	**Title of article:** Effect of simvastatin and/or pioglitazone on insulin resistance, insulin secretion, adiponectin, and proinsulin levels in nondiabetic patients at cardiovascular risk - the PIOSTAT Study. Forst T, Pfützner A, Lübben G, Weber M, Marx N, Karagiannis E, Koehler C, Baurecht W, Hohberg C, Hanefeld M. *Metabolism.* 2007 Apr; 56(4):491-6.

Drug Classes compared in the study: cholesterol lowering drug simvastatin and pioglitazone in randomized trial.
IR2Dx TIGAR™ Markers used in the trial: adiponectin, intact proinsulin and postprandial intact proinsulin.

Abstract

We investigated the effect of pioglitazone in comparison with and in combination with simvastatin on insulin resistance, plasma adiponectin, postprandial plasma glucose, insulin and intact proinsulin levels in a nondiabetic population at cardiovascular risk. One hundred twenty-five nondiabetic patients at cardiovascular risk were randomized to pioglitazone (PIO), pioglitazone and simvastatin (PIO/SIM) or simvastatin (SIM) treatments. Blood samples were taken for the measurement of adiponectin and lipid levels. In addition, an oral glucose load with the measurements of glucose, insulin, and intact proinsulin levels was performed. Adiponectin levels increased from 14.0+/-8.2 to 27.6+/-14.5 microg/mL (P<.0001) during PIO treatment and from 11.7+/-10.0 to 26.7+/-15.7 microg/mL (P<.0001) during PIO/SIM treatment. A decrease in adiponectin levels from 15.5+/-12.7 to 11.6+/-7.0 microg/mL (P<.05) was observed during SIM treatment.

Although fasting intact proinsulin levels remained unchanged, the increase in postprandial intact proinsulin levels could be reduced from 29.5+/-21.4 to 22.1+/-17.5 pmol/L (P<.01) during PIO treatment and from 24.3+/-27.4 to 21.1+/-16.5 mmol/L (P<.05) during PIO/SIM treatment. Lipid parameters improved during SIM treatment but not during PIO treatment. Combined treatment with PIO/SIM was superior in improving overall cardiovascular risk profile than every single drug.

(5)	**Title of article:** Anti-inflammatory effects of pioglitazone and /or simvastatin in high cardiovascular risk patients with elevated high sensitivity C-reactive protein: the PIOSTAT Study. Hanefeld M, Marx N, Pfützner A, Baurecht W, Lübben G, Karagiannis E, Stier U, Forst T. *J Am Coll Cardiol.* 2007 Jan 23;49(3):290-7.

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Drug Classes compared in the study: cholesterol lowering drug simvastatin and pioglitazone in randomized trial.
IR2Dx TIGAR™ Markers used in the trial: hsCRP and HOMA assessment, which includes insulin.
The same data set as the study above with 125 patients looking at Homeostasis model assessment that included fasting insulin and fasting glucose in the assessment, hsCRP and other cardiovascular markers MMP-9 and PAI-1.

Abstract

OBJECTIVES: The purpose of this study was to test the safety and efficacy of pioglitazone and simvastatin in combination versus each drug individually in non-diabetic subjects with cardiovascular disease (CVD) and elevated high-sensitivity C-reactive protein (hs-CRP) levels.

BACKGROUND: Low-grade inflammation is a pathogenic factor for atherosclerosis. High-sensitivity CRP, matrix metalloproteinase (MMP)-9, and plasminogen activator inhibitor (PAI)-1 are markers of inflammation. Statins and peroxisome proliferator-activated receptor (PPAR)-gamma agonists lower inflammatory markers and reduce CVD in type 2 diabetes.

METHODS: In a 12-week, prospective, double-blind trial, 125 subjects were randomized to simvastatin or pioglitazone plus placebo or a simvastatin/pioglitazone combination. We tested changes in hs-CRP by analysis of covariance. A subgroup analysis was performed in patients with and without the metabolic syndrome (MetS). The correlation between changes in hs-CRP and homeostasis model assessment (HOMA; a measure of insulin resistance) was calculated with the Spearman's rank test.

RESULTS: At baseline, there were no significant between-group differences. At 12 weeks, pioglitazone and simvastatin monotherapies significantly reduced hs-CRP (3.64 +/- 2.42 mg/1 to 2.48 +/- 1.77 mg/1 and 3.26 +/- 2.02 mg/1 to 2.81 +/- 2.11 mg/1) and the combination regimen had an additive effect (from 3.49 +/- 1.97 mg/1 to 2.06 +/-1.42 mg/1, $p < 0.001$). For subgroups, the difference between monotherapy and combination therapy was only significant for simvastatin versus simvastatin plus pioglitazone in patients without MetS. Homeostasis model assessment decreased in those receiving pioglitazone, and the correlation between changes in HOMA and hs-CRP was significant ($r = 0.43$; $p < 0.05$). The PAI-1 decreased significantly in the pioglitazone groups only,

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and MMP-9 was also significantly lowered in the pioglitazone groups. No treatment-related serious adverse events occurred in any group.

CONCLUSIONS: Pioglitazone, probably by reducing insulin resistance, has additive anti-inflammatory effects to simvastatin in non-diabetic subjects with CVD and high hs-CRP.

(6) **Title of article**: Investigation of the vascular and pleiotropic effects of atorvastatin and pioglitazone in a population at high cardiovascular risk. Forst T, Wilhelm B, Pfützner A, Fuchs W, Lehmann U, Schaper F, Weber M, Müller J, Konrad T, Hanefeld M. *Diab Vasc Dis Res* 2008 Nov; 5(4):298-303.

Drug Classes compared in the study: cholesterol lowering drug, atorvastatin and insulin sensitizer pioglitazone.
IR2Dx TIGAR™ Markers used in the trial: hsCRP, adiponectin and intact proinsulin.

Abstract

We investigated the effect of atorvastatin monotherapy and combined treatment with atorvastatin and pioglitazone on intima-media thickness, vascular function and the cardiovascular risk profile. In all, 148 patients (76 males, 72 females; aged 61.4+/-6.5 years; body mass index [BMI] 29.2+/-4.1 kg/m^2; mean+/- SD) with increased cardiovascular (CV) risk factors were randomized. Intima-media thickness (IMT), the augmentation index (Aix@75), the microvascular response to acetylcholine, (LDF), lipid status, and plasma levels of intact proinsulin, adiponectin, interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), sCD40L, P-selectin, tissue plasminogen activator (t-PA) and blood lipids were monitored over six months. Atorvastatin treatment, alone and in combination with pioglitazone, revealed a significant regression in IMT (0.923+/-0.013 to 0.874+/-0.012 mm and 0.921+/-0.015 to 0.882+/-0.015 mm; mean+/- SEM; $p<0.05$ respectively) and Aix@75 (27.3+/-1.2 to 25.9+/-1.4; and 25.6+/-1.4 to 24.8+/-1.7%; $p<0.05$). The endothelial response to acetylcholine as measured by laser Doppler fluximetry (LDF) improved during combined treatment (373+/-57 to 576+/-153 AU; $p<0.05$). Addition of pioglitazone to atorvastatin resulted in significant further effects on high-sensitivity C-reactive protein (hsCRP), t-PA, P-selectin, adiponectin, triglycerides and high-density lipoprotein (HDL) cholesterol ($p<0.05$ respectively). Atorvastatin significantly improved IMT and vascular elasticity. Co-administration of pioglitazone provided additional effect on endothelial function, lipid profile and laboratory markers of inflammation.

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(7) **Title of Article:** Long-Term Safety, Tolerability, and Weight Loss Associated with Metformin in the Diabetes Prevention Program Outcomes Study. Bray GA, Edelstein SL, Crandall JP, Aroda VR, Franks PW, Fujimoto W, Horton E, Jeffries S, Montez M, Mudaliar S, Pi-Sunyer XF, White NH, Knowler WC. *Diabetes Care* 2012 Apr; 35(4): 731-737.

Drug Classes compared in the study: Metformin or placebo.
IR2Dx TIGAR™ Markers used in the trial: HbA1c.

Abstract

OBJECTIVE: Metformin produced weight loss and delayed or prevented diabetes in the Diabetes Prevention Program (DPP). We examined its long-term safety and tolerability along with weight loss, and change in waist circumference during the DPP and its long-term follow-up.

RESEARCH DESIGN AND METHODS: The randomized double-blind clinical trial of metformin or placebo followed by a 7–8-year open-label extension and analysis of adverse events, tolerability, and the effect of adherence on change in weight and waist circumference.

RESULTS: No significant safety issues were identified. Gastrointestinal symptoms were more common in metformin than placebo participants and declined over time. During the DPP, average hemoglobin and hematocrit levels were slightly lower in the metformin group than in the placebo group. Decreases in hemoglobin and hematocrit in the metformin group occurred during the first year following randomization, with no further changes observed over time. During the DPP, metformin participants had reduced body weight and waist circumference compared with placebo (weight by 2.06 ± 5.65% vs. 0.02 ± 5.52%, P< 0.001, and waist circumference by 2.13 ± 7.06 cm vs 0.79 ± 6.54 cm, P< 0.001 in metformin vs. placebo, respectively). The magnitude of weight loss during the 2-year double-blind period was directly related to adherence (P< 0.001). Throughout the unblinded follow-up, weight loss remained significantly greater in the metformin group than in the placebo group (2.0 vs. 0.2%, P < 0.001), and this was related to the degree of continuing metformin adherence (P < 0.001).

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CONCLUSIONS: Metformin used for diabetes prevention is safe and well tolerated. Weight loss is related to adherence to metformin and is durable for at least 10 years of treatment.

(8) **Title of Article:** Effects of liraglutide in the treatment of obesity: a randomized, double-blind, placebo controlled study. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, and Lean MEJ. *The Lancet*, Vol. 374, No. 9701, 1606-1616; 7 Nov 2009.

Drug Classes compared in the study: liraglutide alone at different strengths vs. orlistat vs. placebo.
IR2Dx TIGAR™ Markers used in the trial: Not available.

Abstract

BACKGROUND: The frequency of obesity has risen dramatically in recent years but only few safe and effective drugs are currently available. We assessed the effect of liraglutide on bodyweight and tolerability in obese individuals without type 2 diabetes.

METHODS: We did a double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator in 19 sites in Europe. 564 individuals (18–65 years of age, body-mass index 30–40 kg/m^2) were randomly assigned, with a telephone or web-based system, to one of four liraglutide doses (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg, n=90–95) or to placebo (n=98) administered once a day subcutaneously, or orlistat (120 mg, n=95) three times a day orally. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial, including the 2-week run-in. Weight change analysed by intention to treat was the primary endpoint. An 84-week open-label extension followed. This study is registered with ClinicalTrials.gov, number NCT00422058.

FINDINGS: Participants on liraglutide lost significantly more weight than did those on placebo (p=0·003 for liraglutide 1·2 mg and p<0·0001 for liraglutide 1·8–3·0 mg) and orlistat (p=0·003 for liraglutide 2·4 mg and p<0·0001 for liraglutide 3·0 mg). Mean weight loss with liraglutide 1·2–3·0 mg was 4·8 kg, 5·5 kg, 6·3 kg, and 7·2 kg compared with 2·8 kg with placebo and 4·1 kg with orlistat, and was 2·1 kg (95% CI 0·6–3·6) to 4·4 kg (2·9–6·0) greater than that with placebo. More individuals (76%, n=70) lost more than 5% weight with liraglutide 3·0 mg then with placebo (30%, n=29) or orlistat (44%,

n=42). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84–96% reduction) with 1·8–3·0 mg per day. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo, but adverse events were mainly transient and rarely led to discontinuation of treatment.

INTERPRETATION: Liraglutide treatment over 20 weeks is well tolerated, induces weight loss, improves certain obesity-related risk factors, and reduces prediabetes.

(9) **Title of Article:** A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halperm A, Krempf M, Lau DCW, le Roux CW, Ortiz RV, Jensen CB and Wilding JPH. *New Engl J Med* 2015; 373-:11-22 Jul 2, 2015.

Drug Classes compared in the study: non-diabetic patients randomized to either 3.0 mg liraglutide daily injections or placebo.
IR2Dx TIGAR™ Markers used in the trial: glycated HbA1c, hsCRP, insulin, C-peptide and adiponectin.

Abstract

BACKGROUND: Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. Liraglutide, a glucagon-like peptide-1 analogue, has been shown to have potential benefit for weight management at a once-daily dose of 3.1 mg injected subcutaneously.

METHODS: We conducted a 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes and who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension. We randomly assigned patients in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients); both groups received counseling on lifestyle modification. The coprimary end points were the change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight.

RESULTS: At baseline, the mean (±SD) age of the patients was 45.1±12.0 years, the mean weight was 106.2±21.4 kg, and the mean BMI was 38.3±6.4; a total of 78.5% of the patients were women and 61.2% had prediabetes. At week 56, patients in the liraglutide

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group had lost a mean of 8.4±7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8±6.5 kg (a difference of -5.6 kg; 95% confidence interval, -6.0 to -5.1; P<0.001, with last-observation carried-forward imputation). A total of 63.2% of the patients in the liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (P<0.001), and 33.1% and 10.6%, respectively, lost more than 10% of their body weight (P<0.001). The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhea. Serious events occurred in 6.2% of the patients in the liraglutide group and in 5 .0% of the patients in the placebo group.

CONCLUSIONS: In this study, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control. (Funded by Novo Nordisk;
SCALE Obesity and Prediabetes NN8022-1839 ClinicalTrials.gov number, NCT01272219.)

(10) **Title of Article:** Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. Defronzo RA, Tripathy D, Schwenke DC, Musi N, Reaven PD, et. al. *The N. Engl. Journ. Of Med.* 2011;364;12 1104-15

Drug Classes compared in the study: pioglitazone vs. placebo
IR2Dx TIGAR™ Markers used in the trial: HbA1c and insulin

Abstract

BACKGROUND: Impaired glucose tolerance is associated with increased rates of cardiovascular disease and conversion to type 2 diabetes mellitus. Interventions that may prevent or delay such occurrences are of great clinical importance.

METHODS: We conducted a randomized, double-blind, placebo-controlled study to examine whether pioglitazone can reduce the risk of type 2 diabetes mellitus in adults with impaired glucose intolerance. A total of 602 patients were randomly assigned to receive pioglitazone or placebo. The median follow-up period was 2.4 years. Fasting glucose was measured quarterly, and oral glucose tolerance tests were performed annually. Conversion to diabetes was confirmed on the basis of the results of repeat testing.

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RESULTS: Annual incidence rates for type 2 diabetes mellitus were 2.1% in the pioglitazone group and 7.6% in the placebo group, and the hazard ratio for conversion to diabetes in the pioglitazone group was 0.28 (95% confidence interval 0.016 to 0.49; P<0.001). Conversion to normal glucose tolerance occurred in 48% of patients in the pioglitazone group and 28% of those in the placebo group (P<0.001). Treatment with pioglitazone as compared with placebo was associated with significantly reduced levels of fasting glucose (a decrease of 11.7 mg per deciliter vs. 8.1 per deciliter [0.7 mmol per liter vs. 0.5 mmol per liter], P<0.001) 2-hour glucose (a decrease of 30.5 mg per deciliter vs. 15.6 mg per deciliter [1.6 mmol per liter vs. 0.9 mmol per liter], P<0.001), and HbA1c (a decrease of 0.04 percentage points vs. an increase of 0.20 percentage points, P<0.001) Pioglitazone therapy was also associated with a decrease in diastolic blood pressure (by 2.0 mm Hg vs. 0.0 mm Hg, P=0.030), a reduced rate of carotid intima-media thickening (31.5%, P=0.047), and a greater increase in the level of high-density lipoprotein cholesterol (by 7.35 mg per deciliter vs. 4.5 mg per deciliter [0.4 mmol per liter vs. 0.3 mmol per liter], P=0.008). Weight gain was greater with pioglitazone than with placebo (3.9 kg vs. 0.77 kg, P<0.001), and edema was more frequent (12.9% vs. 6.4%, P=0.007).

CONCLUSIONS: As compared with placebo, pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% but was associated with significant weight gain and edema. (Funded by Takeda Pharmaceuticals and others; Clinical Trials.gov, NCT00220961.)

(11) **Title of Article:** Pioglitazone slows Progression of Atherosclerosis in Prediabetes Patients Independent of Changes in Cardiovascular Risk Factors. Saremi A, Schwenke DC, Buchanan TA, Hodis HN, Mack WJ, Banerji MA, Bray GA, Clement SC, Henry RR, Kitabchi AE, Mudaliar S, Ratner RE, Stentz FB, Musi N, Tripathy D, DeFronzo RA, Reaven PD. Ather., Thromb. & Vascul. Biol. 2013; 33:393-399

Drug Classes compared in the study: pioglitazone vs. placebo
IR2Dx TIGAR™ Markers used in the trial: HbA1c, adiponectin, hsCRP and insulin

Abstract

OBJECTIVE: To determine whether changes in standard and novel risk factors during the Actos Now for Prevention of Diabetes trial explained the slower rate of carotid intima media thickness (CIMT) progression with pioglitazone treatment in persons with prediabetes.

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METHODS AND RESULTS: CIMT was measured in 382 participants at the beginning and up to 3 additional times during follow-up of the Actos Now for Prevention of Diabetes trial. During an average follow-up of 2.3 years, the mean unadjusted annual rate of CIMT progression was significantly (p=0.01) lower with pioglitazone treatment ($4.76x10^{-3}$ mm/year; 95% CI: $2.39x10^{-3}$-$7.14x10^{-3}$ mm/year) compared with placebo ($9.69x10^{-3}$ mm/year; 95% CI: $7.24x10^{-3}$-$12.15x10^{-3}$ mm/year). High-density lipoprotein cholesterol, fasting and 2-hour glucose, HbA1c, fasting insulin, Matsuda insulin sensitivity index, adiponectin, and plasminogen activator inhibitor-1 levels improved significantly with pioglitazone treatment compared with placebo (P<0.001). However, the effect of pioglitazone on CIMT progression was not attenuated by multiple methods of adjustment for traditional, metabolic, and inflammatory risk factors and concomitant medications, and was independent of changes in risk factors during pioglitazone treatment.

CONCLUSIONS: Pioglitazone slowed progression of CIMT, independent of improvement in hyperglycemia, insulin resistance, dyslipidemia, and systemic inflammation in prediabetes. These results suggest a possible direct vascular benefit of pioglitazone.

(12) **Title of Article:** Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM Randomised Trial. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; Lancet 2002 Jun 15; 359(9323):2072-7

Drug Classes compared in the study: acarbose vs. placebo
IR2Dx TIGAR™ Markers used in the trial: None, this is an older study with the first antidiabetic drug to be tested in prediabetes patients in a major randomized and controlled clinical trial. It is represented here as an option for such patients not controlled with diet and exercise. Obviously, there are now better drug options for these patients and since no further major trials have been conducted with acarbose it is unknown how this drug may or may not positively affect underlying markers of metabolic control.

Abstract

BACKGROUND: The worldwide increase in type 2 diabetes mellitus is becoming a major health concern. We aimed to assess the effect of acarbose in preventing or delaying conversion of impaired glucose tolerance to type 2 diabetes.

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METHODS: In a multicentre, placebo-controlled randomised trial, we randomly allocated patients with impaired glucose tolerance to 100 mg acarbose or placebo three times daily. The primary endpoint was development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT). Analyses were by intention to treat.

FINDINGS: We randomly allocated 714 patients with impaired glucose tolerance to acarbose and 715 to placebo. We excluded 61 (4%) patients because they did not have impaired glucose tolerance or had no postrandomisation data. 211 (31%) of 682 patients in the acarbose group and 130 (19%) of 686 on placebo discontinued treatment early. 221 (32%) patients randomised to acarbose and 285 (42%) randomised to placebo developed diabetes (relative hazard 0.75 [95% CI 0.63-0.90]; p=0.0015). Furthermore, acarbose significantly increased reversion of impaired glucose tolerance to normal glucose tolerance (p<0.0001). At the end of the study, treatment with placebo for 3 months was associated with an increase in conversion of impaired glucose tolerance to diabetes. The most frequent side-effects to acarbose treatment were flatulence and diarrhea.

INTERPRETATION: Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance.

(13) **Title of Article**: Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. Keman WN, Viscoli CM, Young LH, Inzuchhi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D & Winder TR, for the IRIS Trial Investigators. N Engl J Med. 2016 Apr 7; 374(14): 1321-1331.

Drug Classes compared in the study: Type 2 diabetes patients received standard of care therapy plus pioglitazone or placebo
IR2Dx TIGAR™ Markers used in the trial: Fasting plasma insulin, hsCRP and HbA1c

Abstract

BACKGROUND: Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that

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pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS: In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance based on a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

RESULTS: By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P = 0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P = 0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P < 0.001), edema (35.6% vs. 24.9%, P < 0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P = 0.003).

CONCLUSIONS: In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke: Clinical Trials.gov number, NCT00091949.)