Comparing the effects of insulin glargine and thiazolidinediones on plasma lipids in type 2 diabetes: a patient-level pooled analysis

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Abstract

Background  The prevalence of dyslipidaemia and the risk of cardiovascular disease are elevated in patients with type 2 diabetes. This analysis compared the effects of insulin glargine versus thiazolidinediones (TZDs) on lipid profiles.

Methods  Patient-level data were pooled from two randomized clinical studies. The population included 552 men and women aged >18 years, diagnosed with type 2 diabetes for at least 6 months, on metformin and/or sulphonylurea, and with A1C ≥7.5% and <12.0% at screening. Lipid outcome measures included change from baseline in lipid levels [low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol, triglycerides, and free fatty acids] and attainment of lipid goals for LDL-C, non-HDL-C, and triglycerides.

Results  Both insulin glargine and TZDs improved lipid profiles from baseline values. Compared with TZDs, treatment with insulin glargine led to 7.9% greater reduction in LDL-C (p < 0.0003), 7.5% greater reduction in non-HDL-C (p < 0.0001), and 7.8% greater reduction in total cholesterol (p < 0.0001), whereas the HDL-C increase with TZD was 7.6% greater than that with insulin glargine (p < 0.0001). The percentage of patients attaining the lipid goals was comparable between insulin glargine and pioglitazone, but lower for rosiglitazone. Insulin glargine improved glycaemic control more than TZDs; however, insulin glargine caused more hypoglycaemia. Treatment with TZDs caused more weight gain and peripheral oedema.

Conclusion  These findings suggest that the favourable effects of insulin glargine on plasma lipid profiles should be considered among the advantages of treatment with insulin glargine as they are for TZDs. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords  insulin glargine; lipids; thiazolidinediones; type 2 diabetes

Introduction

It is well established that the prevalence of dyslipidaemia and the risk of cardiovascular disease (CVD) are greater in patients with type 2 diabetes than in the general population [1–4]. Elevated plasma lipid concentrations are well-recognized risk factors for CVD, and reducing them to the values recommended by the American Diabetes Association (ADA) and the American Heart
Association (AHA) is a primary strategy in CVD prevention in individuals with type 2 diabetes [1,5–7]. Thus, the effect of antihyperglycaemic therapies on lipid parameters merits consideration in the treatment of type 2 diabetes patients.

Over the years, insulin was suspected to be atherogenic [8–10], whereas thiazolidinediones (TZDs) were considered to have cardioprotective potential [11,12]. These properties have been regarded to contribute to the unfavourable effects of insulin and beneficial effects of TZDs on lipids [13,14]. However, clinical studies indicate that insulin therapy produces favourable effects on plasma lipid concentrations in patients with type 2 diabetes [15–18]. In particular, treatment with insulin glargine has been associated with improvement in the levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and triglycerides (TGs) [15,16,18]. Therefore, to investigate in greater detail the comparative effects of insulin glargine, rosiglitazone, and pioglitazone on lipoprotein and glycaemic parameters, we identified two randomized clinical studies that compared insulin glargine with a TZD in the treatment of type 2 diabetes [19,20]. Although these studies were designed primarily to evaluate glycaemic control, lipoprotein levels were also determined [19,20]. One study compared insulin glargine with rosiglitazone [19], and another study compared insulin glargine with pioglitazone [20]. The pooled analysis suggests that insulin glargine has positive effects on several lipoprotein parameters often seen elevated in this population, and confirms the known effects of TZDs on lipids [19,20].

Materials and methods

Participant-level data were pooled from two previously published randomized studies comparing the efficacy, safety, and tolerability of insulin glargine versus a TZD, either pioglitazone or rosiglitazone, in type 2 diabetes. These studies [19,20] were selected for analysis because they had similar patient profiles, included thorough measurement of lipid parameters, and compared the effects of insulin glargine with one of the two TZDs available at the time of the study. Each study used a randomized, parallel-group, two-arm, open-label design with outcome measurements after 24 weeks of treatment. The participants included men and women aged >18 years, diagnosed with type 2 diabetes for at least 6 months, on metformin and/or sulphonylurea, and with A1C ≥7.5% and <12.0% at screening.

The participants in the analysis were randomized patients who had baseline measurements, received at least one dose of study medication, and had outcome measurements from at least one follow-up visit. Patient-level data from the 552 participants who met these criteria were included in the pooled analysis.

Treatments

Patients were randomized to insulin glargine titrated to a fasting plasma glucose (FPG) goal of <5.55 mmol/L (<100 mg/dL) or to a TZD comparator level (pioglitazone or rosiglitazone) [19,20]. Detailed information regarding treatment procedure is available in prior publications [19,20]. Study protocols were approved by the respective independent review boards, and both studies were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from study participants prior to any treatment initiation.

Because of the design of the individual studies, all patients randomized to rosiglitazone also were taking both metformin and a sulphonylurea [19], and all patients receiving pioglitazone were taking either metformin or a sulphonylurea [20]. For patients who were taking a lipid-lowering medication (e.g. statin or fibrate) at study onset, titration of these medications was permitted under the protocol at the discretion of the treating physician.

Outcome measures

The lipid outcome measures for this post hoc analysis were (1) change from baseline in plasma lipid levels: LDL-C, HDL-C, non-HDL-C, TC, TGs, and free fatty acids (FFAs); (2) attainment of ADA/AHA recommended goals for LDL-C [<2.59 mmol/L (<100 mg/dL)], non-HDL-C [<3.37 mmol/L (<130 mg/dL)], and TGs [<1.70 mmol/L (<150 mg/dL)]; and (3) attainment of TC/HDL-C <4.5 and LDL-C/HDL-C <3.5. Glycaemic control was measured by change from baseline in A1C and FPG and proportion of patients achieving A1C ≤7.0%. The safety evaluation included body weight, peripheral oedema, and episodes of symptomatic and severe hypoglycaemia.

Fasting blood samples were collected at baseline and weeks 6, 12, 18, and 24 and were sent for analysis to a central laboratory that participated in the Lipid Standardization Program of the Centers for Disease Control (Covance Central Laboratory Services, Indianapolis, IN). The TC and TG assays were performed using Hitachi analyzers (Hitachi, Ltd, Japan). Direct HDL-C was measured with an enzymatic colorimetric assay (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein cholesterol was calculated using the Friedewald formula (TC – HDL-C – TG/5) [21]. FFAs were measured using the Wako enzymatic non-esterified (free) fatty acids (NEFA) method. The A1C assay was performed on a Bio-Rad Variant ™ Analyzer (Bio-Rad Laboratories, Hercules, CA).

Statistical analysis

Analysis of covariance (ANCOVA) was used to evaluate change from baseline for lipid outcomes, glycaemic outcomes, and weight. Each ANCOVA model included treatment (insulin glargine versus pooled TZD) and study as fixed effects and corresponding baseline level as a
cvariates. To account for the use of lipid-lowering medications, additional ANCOVAs were conducted for change from baseline in each lipid outcome, with treatment (insulin glargine versus pooled TZD) and statin/fibrate use (yes versus no) as fixed effects and lipid baseline level as covariate. Lipid parameters were analysed on a log scale, to adjust for non-normal distributions, and then back-transformed for reporting results. If measurement of an outcome variable was not available at week 24, then the last observation post-baseline was carried forward.

Continuous lipid values measured at baseline were categorized into quartiles. Analysis of variance of change from baseline was conducted for each lipid outcome variable, with treatment and baseline quartile as factors. To compare the effects of the three treatments (insulin glargine, pioglitazone, and rosiglitazone), paired comparisons were made with treatment and baseline quartile as factors. To account for the use of sulphonylurea, background use of metformin, and concomitant use of blood pressure medication, background use of metformin, background use of metformin and sulphonylurea, baseline A1C, baseline FPG, baseline weight, baseline systolic blood pressure, baseline diastolic blood pressure, baseline heart rate, baseline TC, baseline LDL-C, baseline HDL-C, baseline TGs, baseline FFA, change in FPG from baseline, change in A1C from baseline, and change in weight from baseline. A significance level of $p \leq 0.15$ was required for a covariate to enter into the model and $p \leq 0.10$ to be retained in the final model.

### Results

Table 1 shows the demographic and baseline characteristics of the 552 patients included in the pooled analysis. A total of 264 patients were randomized to insulin glargine and 288 patients to TZD (112 to rosiglitazone and 176 to pioglitazone). Not all patients had complete lipid data, so analyses of most lipid outcomes included 258 patients treated with insulin glargine and 278 with TZD (110 rosiglitazone and 168 pioglitazone). Low-density lipoprotein cholesterol values were not calculated for 54 participants (24 insulin glargine, 9 rosiglitazone, 21 pioglitazone) with TGs $>4.52$ mmol/L ($>400$ mg/dL) because LDL-C calculation becomes unreliable under such conditions [21].

### Changes in plasma lipid levels

Changes in lipid parameters are shown in Table 2; adjusted values were controlled for study differences and

#### Table 1. Demographic and baseline characteristics

|                        | Insulin glargine (n = 264) | All TZDs (n = 288) |
|------------------------|-----------------------------|-------------------|
| Age (years)            | 54.2 ± 10.9                 | 53.3 ± 10.7       |
| Female, n (%)          | 134 (50.8)                  | 134 (46.5)        |
| Race, n (%)            |                             |                   |
| White                  | 171 (64.8)                  | 199 (69.1)        |
| Black                  | 51 (19.3)                   | 44 (15.3)         |
| Hispanic               | 32 (12.1)                   | 39 (13.5)         |
| Other                  | 10 (3.8)                    | 6 (2.1)           |
| Duration of diabetes (years) | 7.3 ± 5.5                  | 6.8 ± 4.7         |
| Lipid-reducing therapy, statin or fibrate, n (%) | 103 (39.0) | 107 (37.2) |
| Metformin*             | 90 (34.1)                   | 103 (35.8)        |
| Sulphonylurea*         | 69 (26.1)                   | 73 (25.3)         |
| Metformin + sulphonylurea* | 105 (39.8)                  | 112 (38.9)        |
| Weight (kg)            | 96.8 ± 20.5                 | 97.9 ± 21.1       |
| BMI (kg/m²)            | 34.1 ± 7.8                  | 33.7 ± 6.6        |
| Lipid values, mean ± SE (mg/dL)* |                  |                   |
| LDL-C                  | 109.2 ± 2.12                | 106.7 ± 2.21      |
| HDL-C                  | 42.3 ± 1.46                 | 41.5 ± 1.44       |
| Non-HDL-C              | 151.2 ± 1.74                | 150.5 ± 1.69      |
| Total cholesterol      | 195.6 ± 1.39                | 194.2 ± 1.33      |
| Triglycerides          | 194.3 ± 4.18                | 198.8 ± 3.63      |
| Free fatty acids       | 52.9 ± 2.72                 | 51.2 ± 2.50       |
| Glycaemic values       |                             |                   |
| A1C (%)                | 9.1 ± 1.1                   | 9.1 ± 1.2         |
| FPG (mg/dL)            | 209.1 ± 63.3                | 209.1 ± 61.3³     |

Data are mean ± SD, except where indicated.

BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TZD, thiazolidinedione.

*Because of differences in study design, all 176 TZD patients taking either metformin or a sulphonylurea were treated with pioglitazone, and all 112 TZD patients taking metformin and a sulphonylurea were treated with rosiglitazone.

³Lipid levels reported as geometric means.
Table 2. Changes from baseline in lipid levels, pooled analysis

|                          | Unadjusted | Adjusteda |
|--------------------------|------------|-----------|
|                          | Baselineb | Endpointb | Change from baseline (%) | Change from baseline (%) | Difference in change from baseline (%) | p value |
| LDL-C (mg/dL)            |           |           |                        |                          |                                     |         |
| Insulin glargine         | 109.21 ± 2.1 | 105.92 ± 2.1 | −3.01 ± 1.7 | −1.9 | −7.9 | 0.0003 |
| TZD                     | 106.67 ± 2.2 | 113.47 ± 2.0 | 6.37 ± 2.0 | 6.6 | — |         |
| HDL-C (mg/dL)            |           |           |                        |                          |                                     |         |
| Insulin glargine         | 42.29 ± 1.5 | 42.98 ± 1.6 | 0.69 ± 0.9 | 1.1 | −7.6 | <0.0001 |
| TZD                     | 41.46 ± 1.4 | 45.83 ± 1.5 | 10.52 ± 1.2 | 9.4 | — |         |
| Non-HDL-C (mg/dL)        |           |           |                        |                          |                                     |         |
| Insulin glargine         | 151.20 ± 1.7 | 140.92 ± 1.7 | −6.80 ± 1.3 | −5.9 | −7.5 | <0.0001 |
| TZD                     | 150.50 ± 1.7 | 151.74 ± 1.8 | 0.82 ± 1.6 | 1.7 | — |         |
| Total cholesterol (mg/dL)|           |           |                        |                          |                                     |         |
| Insulin glargine         | 195.58 ± 1.4 | 186.20 ± 1.3 | −4.80 ± 1.0 | −4.2 | −7.8 | <0.0001 |
| TZD                     | 194.24 ± 1.3 | 201.10 ± 1.3 | 3.53 ± 1.3 | 4.0 | — |         |
| Triglycerides (mg/dL)    |           |           |                        |                          |                                     |         |
| Insulin glargine         | 194.27 ± 4.2 | 156.22 ± 4.0 | −19.59 ± 2.8 | −18.5 | −6.5 | 0.0504 |
| TZD                     | 198.79 ± 3.6 | 169.64 ± 3.5 | −14.66 ± 2.7 | −12.8 | — |         |
| Free fatty acids (mg/dL) |           |           |                        |                          |                                     |         |
| Insulin glargine         | 52.92 ± 2.7 | 38.32 ± 3.0 | −27.59 ± 3.5 | −25.8 | −7.3 | 0.0528 |
| TZD                     | 51.15 ± 2.5 | 40.89 ± 2.8 | −20.05 ± 3.3 | −20.0 | — |         |

Data are mean ± SE.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TZD, thiazolidinedione.
aAdjusted for study and baseline lipid concentration.
bGeometric means.

decision to determine whether the changes observed in lipid parameters varied by baseline concentration. Changes from baseline were analysed by baseline quartile and treatment (insulin glargine, rosiglitazone, or pioglitazone) for each lipid parameter (Figure 1). Improvement in lipid levels differed significantly depending on baseline concentration (p < 0.0001 for LDL-C, non-HDL-C, TC, TGs, and FFAs; p = 0.0252 for HDL-C), with the greatest improvement generally observed among patients who had the most abnormal lipid concentrations at baseline. For example, treatment with insulin glargine or pioglitazone produced an average decrease in LDL-C of more than 20 mg/dL among patients in the highest quartile at baseline; however, patients in the lower two quartiles experienced a modest increase. Significant treatment differences were obtained for LDL-C (p < 0.0001), HDL-C (p < 0.0001),...
Table 3. Changes in lipid levels by statin/fibrate use, pooled analysis

|                         | Insulin glargine versus pooled TZD* | Statin/fibrate therapy | No statin/fibrate therapy |
|-------------------------|-------------------------------------|------------------------|---------------------------|
|                         | p value                              | % Change               | % Change                  |
| LDL-C                   | 0.0003                              | −5.51 ± 3.73           | −1.55 ± 1.69              |
| Insulin glargine        |                                     | 8.10 ± 4.11            | 5.44 ± 2.08               |
| TZD                     |                                     | 2.76 ± 1.37            | 0.90 ± 1.11               |
| HDL-C                   | <0.0001                             | 11.67 ± 1.51           | 9.84 ± 1.68               |
| Insulin glargine        |                                     | −9.07 ± 2.62           | −5.29 ± 1.33              |
| TZD                     |                                     | −0.97 ± 3.24           | 1.93 ± 1.67               |
| Non-HDL-C               | <0.0001                             | −6.30 ± 1.93           | −3.80 ± 1.09              |
| Insulin glargine        |                                     | 2.44 ± 2.55            | 4.20 ± 1.32               |
| TZD                     |                                     | −23.16 ± 5.01          | −17.16 ± 3.41             |
| Total cholesterol       | 0.0015                              | −21.11 ± 5.20          | −10.50 ± 3.01             |
| Triglycerides           | 0.0641                              | −27.08 ± 5.50          | −27.93 ± 4.54             |
| Insulin glargine        |                                     | −18.05 ± 5.99          | −21.23 ± 3.89             |
| Free fatty acids        | 0.0547                              |                       |                           |
|                         |                                     |                       |                           |

Data are mean ± SE.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TZD, thiazolidinedione.
*Adjusted for statin/fibrate use and baseline lipid concentration.

non-HDL-C (p < 0.0001), TC (p < 0.0001), and TGs (p = 0.0298). Insulin glargine was better than rosiglitazone in reducing LDL-C (p < 0.0001), non-HDL-C (p < 0.0001), TC (p < 0.0001), and TGs (p = 0.0361). Pioglitazone produced greater improvement than did rosiglitazone in LDL-C (p < 0.0001), HDL-C (p < 0.0001), non-HDL-C (p < 0.0001), TC (p < 0.0001), and TGs (p = 0.0094). Insulin glargine and pioglitazone produced comparable benefits, except for greater reduction in TC with insulin glargine (p = 0.0481) and greater improvement in HDL-C with pioglitazone (p < 0.0001). Overall, both insulin glargine and pioglitazone had beneficial effects on lipid concentrations; however, rosiglitazone had deleterious effects on LDL-C, non-HDL-C, and TC.

Using stepwise regression models, we examined various factors (covariates) that could serve as predictors of changes in lipid levels in this pooled analysis. The amount of variability in lipid measures that was explained by each covariate is presented in Table 4. Baseline lipid concentration explained the largest amount of variability for each lipid parameter except HDL-C; however, no other covariate accounted for more than 5% of the variability for any lipid level. Differences between insulin glargine and pooled TZD treatment were significant predictors for LDL-C, HDL-C, non-HDL-C, TC, and TGs. For each lipid parameter except HDL-C, insulin glargine was associated with greater improvement in lipid outcomes. Baseline A1C, baseline weight, change in A1C, and change in weight did not account for the variability in any lipid parameter except FFA.

Changes in glycaemic control

Both insulin glargine (adjusted mean ± SE Δ = −2.04 ± 0.06%; p < 0.0001) and TZDs (adjusted mean ± SE −1.68 ± 0.06%; p < 0.0001) reduced A1C, with insulin glargine producing a greater reduction in A1C than TZDs (mean ± SE difference = −0.36 ± 0.09%; p < 0.0001); however, the difference was not significant for patients with BMI > 35 kg/m². Both treatment groups also yielded significant reductions in FPG [insulin glargine: adjusted mean ± SE Δ = 4.51 ± 0.16 mmol/L (−81.33 ± 2.9 mg/dL), p < 0.0001; TZD: adjusted mean ± SE Δ = −3.21 ± 0.16 mmol/L (−57.91 ± 2.8 mg/dL), p < 0.0001]. Improvement in FPG was significantly greater with insulin glargine than with TZD therapy [mean ± SE difference = −1.30 ± 0.22 mmol/L (−23.42 ± 3.9 mg/dL), p < 0.0001], although the difference was not significant for patients with BMI > 40 kg/m². Fifty percent of patients treated with insulin glargine and 42% of patients in the pooled TZD group achieved A1C ≤ 7.0% by the end of the treatment.

Safety

Symptomatic hypoglycaemia [defined as symptoms of hypoglycaemia confirmed by a blood glucose level of <3.9 mmol/L (<70 mg/dL)] was reported by 32.6% of patients treated with insulin glargine and 21.9% of patients treated with a TZD. Severe hypoglycaemia [defined as symptomatic hypoglycaemia requiring third-party assistance with a blood glucose level of <2.0 mmol/L (<36 mg/dL) or recovery after oral carbohydrate, intravenous glucose, or glucagon administration] occurred in 2.6% of insulin-glargine-treated and 2.4% of TZD-treated patients. Treatment-related peripheral oedema was reported in 6.6% of TZD-treated and 0% of insulin-glargine-treated patients.

Weight increased in both the insulin glargine (adjusted mean ± SE Δ = 1.83 ± 0.27 kg) and TZD (adjusted mean SE Δ = 2.98 ± 0.26 kg) groups; however, TZD produced significantly greater weight gain (mean ± SE difference = 1.14 ± 0.37 kg; p = 0.0024, compared with glargine).
There was a progressive increase in weight gain across the BMI groups for TZD but not for insulin glargine. The largest difference in weight gain was observed in patients with BMI $\geq 40$ kg/m$^2$ (adjusted mean ± SE difference = $-2.40 \pm 1.10$ kg; $p = 0.0324$). 

**Discussion**

Whereas the effects of TZD on lipids are well known, the effects of insulin on lipids are not generally appreciated; in fact, insulin therapy has been hypothesized to have
deleterious effects on lipids in patients with type 2 diabetes [8–10]. Our analysis shows that insulin glargine treatment results in greater improvement in lipid levels and more patients reaching the ADA/AHA recommended lipid goals compared with pooled TZD treatment in combination with metformin with or without sulphonylureas. The beneficial effects of insulin glargine are greater in patients on lipid-lowering therapy. Generally, the lipid benefits of insulin glargine are comparable with those of pioglitazone and better than those of rosiglitazone. Reductions in A1C and FPG and achievement of A1C ≤7.0% are greater than those observed with pooled TZD treatment, especially for less obese patients. As expected, hypoglycaemia was more common among patients treated with insulin glargine than among those treated with a TZD, but episodes of severe hypoglycaemia were low in both treatment groups.

Previous studies have shown an improvement in lipid profiles of diabetic patients treated with insulin [17,22,23]. Treatment with 70% NPH insulin/30% regular insulin has been shown to reduce TC and TGs in patients with type 2 diabetes [17]. Twenty-four weeks of insulin glargine with standard oral anti-diabetic drug therapy decreases TC, non-HDL-C, and TGs [15]. Insulin glargine or NPH insulin combined with metformin results in a 27% to 29% decrease in TGs and a 5% to 6% increase in HDL-C [18]. The current analysis extends the information in the literature regarding the effects of insulin glargine on all lipid parameters, as well as the lipid ratios and lipid goals achieved in patients with type 2 diabetes.

The effect of TZDs on lipids in this analysis is generally consistent with previous reports on TZDs in patients with type 2 diabetes. In a meta-analysis and in previous studies, pioglitazone has been shown to reduce TGs and LDL-C/HDL-C and increase HDL-C levels [24,25]. Rosiglitazone improves HDL-C; however, its effects on LDL-C and TC are variable [26]. In a prospective randomized clinical study comparing pioglitazone and rosiglitazone in the treatment of patients with type 2 diabetes and dyslipidaemia, significantly better outcomes in TG, HDL-C, and LDL-C levels were reported for pioglitazone than for rosiglitazone [27].

Given the evidence that statins improve clinical outcomes and the large number of patients with elevated LDL-C, non-HDL-C, and TGs at baseline, it was surprising

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**Table 4. Predictors of change in plasma lipid levels per stepwise regression analysis**

| Outcome          | Covariate                                      | Variance explained (%) | \( p \) value |
|------------------|------------------------------------------------|------------------------|---------------|
| LDL-C            | LDL-C at baseline                              | 28.47                  | <0.0001       |
|                  | HDL-C at baseline                              | 2.10                   | 0.0008        |
|                  | Concomitant statin/fibrate use: no versus yes  | 1.83                   | 0.0002        |
|                  | Treatment group: TZD versus insulin glargine   | 1.54                   | 0.0008        |
|                  | Study: rosiglitazone versus pioglitazone       | 1.49                   | 0.0032        |
|                  | Race: nonwhite versus white                    | 0.61                   | 0.0281        |
|                  | Sex: female versus male                        | 0.43                   | 0.0789        |
| HDL-C            | Treatment group: TZD versus insulin glargine   | 6.09                   | <0.0001       |
|                  | Background use of both SU and metformin: no versus yes | 4.60 | 0.0005        |
|                  | HDL-C at baseline                              | 3.00                   | <0.0001       |
|                  | Sex: female versus male                        | 1.59                   | 0.0025        |
|                  | Background SU: no versus yes                   | 0.56                   | 0.0458        |
|                  | Age (years)                                    | 0.47                   | 0.0188        |
|                  | Race: nonwhite versus white                    | 0.52                   | 0.0898        |
| Non-HDL-C        | Total cholesterol at baseline                  | 25.28                  | <0.0001       |
|                  | Study: rosiglitazone versus pioglitazone       | 3.36                   | <0.0001       |
|                  | Treatment group: TZD versus insulin glargine   | 2.64                   | <0.0001       |
|                  | Concomitant statin/fibrate use: no versus yes  | 1.83                   | 0.0002        |
|                  | Race: nonwhite versus white                    | 1.22                   | 0.0036        |
| Total cholesterol| Total cholesterol at baseline                  | 26.71                  | <0.0001       |
|                  | Study: rosiglitazone versus pioglitazone       | 4.31                   | <0.0001       |
|                  | Concomitant statin/fibrate use: no versus yes  | 1.57                   | 0.0005        |
|                  | Race: nonwhite versus white                    | 1.05                   | 0.0186        |
|                  | HDL-C at baseline                              | 0.44                   | 0.0751        |
| Triglycerides    | Triglyceride at baseline                       | 28.61                  | <0.0001       |
|                  | Study: rosiglitazone versus pioglitazone       | 3.83                   | <0.0001       |
|                  | HDL-C at baseline                              | 2.40                   | 0.0001        |
|                  | Race: nonwhite versus white                    | 1.15                   | 0.0036        |
|                  | Treatment group: TZD versus insulin glargine   | 0.76                   | 0.0200        |
|                  | Concomitant statin/fibrate use: no versus yes  | 0.47                   | 0.0631        |
| FFA              | FFA at baseline                                | 50.93                  | <0.0001       |
|                  | A1C at baseline                                | 1.18                   | 0.0092        |
|                  | Diastolic blood pressure at baseline           | 0.76                   | 0.0045        |
|                  | Study: rosiglitazone versus pioglitazone       | 0.78                   | 0.0048        |
|                  | Sex: female versus male                        | 0.48                   | 0.0226        |
|                  | Treatment group: TZD versus insulin glargine   | 0.35                   | 0.0610        |

Note: FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; SU, sulphonylureas; TZD, thiazolidinedione.
Effects of Insulin Glargine versus TZD on Lipids

that more than 60% of patients were not receiving lipid-lowering therapy. It is of interest that insulin glargine produced greater improvement in lipid levels in patients on statins or fibrates, and a greater number of patients on insulin glargine attained the ADA/AHA goals for LDL-C, non-HDL-C, and TGs in this study. It is encouraging that the greatest reduction in LDL-C occurred in patients with the highest baseline levels. However, the finding of increased LDL-C among patients in the lower baseline quartiles reinforces the importance of monitoring patients with elevated risk for cardiovascular disease and providing lipid-lowering therapy when appropriate.

Insulin regulates FFA, TG, and lipoprotein particle metabolism through a variety of mechanisms, which may account for the observed beneficial lipid effects of insulin glargine in this analysis. Insulin suppresses lipolysis, preventing the release of FFAs from adipose tissue [28], and increases the plasma clearance of FFAs [29]; these effects result in a reduction of available substrate for hepatic TG production [28]. Insulin also suppresses the hepatocyte production of TGs and very low density lipoproteins in vitro [30,31] and in vivo [29,32]. Moreover, insulin is a potent activator of lipoprotein lipase, which enhances the catabolism of TG-rich lipoproteins [28]. A significant decrease in hepatic lipase activity also has been observed following insulin therapy, which may reduce the production of highly atherogenic small dense LDL particles [23]. Insulin may promote LDL-C clearance by enhancing LDL degradation [33,34]. Finally, insulin regulates HDL particle synthesis through induction of apolipoprotein A-1 gene expression in the liver [35].

Hyperglycaemia and dyslipidaemia are associated with an increased risk of cardiovascular events in patients with type 2 diabetes [36,37]. Our analysis suggests that insulin has beneficial effects on lipids and glucose in patients with type 2 diabetes. The clinical impact of this observation on cardiovascular risk reduction will be addressed specifically in the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial. This randomized controlled study was designed to evaluate the effects of insulin glargine on cardiovascular risk and mortality in a variety of dysglycaemic patients (i.e. impaired fasting glucose, impaired glucose tolerance, diabetes) who are at high risk for a cardiovascular event [38]. Therefore, the findings of this study will be applicable to a broad spectrum of patients with glycaemic abnormalities [38].

The choice of antihyperglycaemics should be individualized according to the patient's medical history, disease characteristics, comorbidities, baseline A1C, lifestyle, body weight, and risk of adverse events. Insulin glargine might be more appropriate for patients requiring a greater reduction in A1C whereas TZD might be more appropriate for patients with a history of severe hypoglycaemia. On the basis of our study, either insulin glargine or pioglitazone can be chosen if additional benefits on lipids are a consideration for choosing an antihyperglycaemic agent. Insulin glargine might be more appropriate, for instance, in patients taking a lipid-lowering medication, in light of the synergistic effects of statins and insulin glargine observed in this study, whereas pioglitazone may be preferred if HDL is very low. Either insulin glargine or pioglitazone may be beneficial in patients at risk for cardiovascular disease.

Analysis limitations

This analysis pooled results from studies of rosiglitazone and pioglitazone [19,20], which are known to have different effects on lipid parameters [39,40]. The lipid results, therefore, are presented separately for rosiglitazone and pioglitazone. Glycaemic outcomes are presented only for pooled TZD treatment because TZDs have similar glycaemic effects [39,40]. Differences attributable to other antidiabetic agents cannot be evaluated, as participants in the rosiglitazone study received both metformin and a sulphonylurea [19] whereas participants in the pioglitazone study received either one or the other [20]. However, TZD use accounted for variability only in HDL-C in the lipid regression models. Furthermore, doses of statin and fibrate medications were not held constant during treatment. The possibility that potential dosage titrations of these lipid-lowering medications contributed to the observed lipid effects cannot be excluded. A future comparative study of insulin glargine versus pioglitazone, with the addition of more detailed lipid measurements, such as apolipoproteins and small dense LDL particles, and with statin dose held constant during the treatment period, would provide further insight into the lipid-lowering effects of these two medications.

Safety

The higher frequency of episodes of hypoglycaemia with insulin glargine and weight gain and peripheral oedema with TZD in our analysis are consistent with the known side effects of these agents. Episodes of severe hypoglycaemia occurred in fewer than 3% of patients receiving either treatment [19,20].

Conclusion

Treatment with insulin glargine showed beneficial effects on lipid parameters, which are generally comparable with the effects of pioglitazone and more favourable than those of rosiglitazone. Lipid improvement occurred within the context of better glycaemic control attained with insulin glargine. Insulin glargine treatment led to more hypoglycaemia but less weight gain and oedema compared with TZD treatment. Both insulin glargine and TZDs promoted changes in lipid profile; however, there were some specific qualitative and quantitative differences depending on the agent used to lower blood glucose. These findings suggest that favourable effects on plasma lipid profiles should be considered among the advantages of treatment with insulin glargine as they are for TZDs.
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Conflict of interest

Dr. Chaudhuri has received research support from, and is a consultant and on the advisory panel for, the Sanofi-aventis US Group. He is on the speakers’ bureau for Eli Lilly and Company, Merck & Co., Inc., Novo Nordisk Inc., and Sano Pharmaceutical Corporation, and the Sanofi-aventis US Group. Dr. Rosenstock has served on scientific advisory boards and received honoraria/consulting fees from Amylin Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Daiichi Sankyo Co., Ltd., Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, MannKind Corporation, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc, Roche, Sanofi-aventis US, and Takeda Pharmaceuticals North America, Inc. He has also received grants/research support from Amylin Pharmaceuticals, Inc., AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Daiichi Sankyo Co., Ltd., Eli Lilly and Company, Forest Laboratories, Inc., GlaxoSmithKline, Johnson & Johnson, MannKind Corporation, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc, Roche, Sanofi-aventis US, and Takeda Pharmaceuticals North America, Inc. Dr. DiGenio is an employee of Sanofi-aventis US. Dr. Meneghini has received research support from MannKind Corporation and Pfizer Inc, has served as an advisor and consultant to Novo Nordisk Inc, and has received honoraria for speakers bureau from Amylin Pharmaceuticals, Inc., Eli Lilly and Company, Novo Nordisk Inc., and Sanofi-aventis US. Dr. Hollander has nothing to disclose. Dr. McGill is on the advisory panel for Abbott, Merck & Co., Inc., Novo Nordisk Inc., Shionogi, and the Sanofi-aventis US Group, and is a consultant for Boehringer Ingelheim Pharmaceuticals, Inc. She has received research support from Amylin Pharmaceuticals, Inc., An-dromeda, CPEX, Forest Laboratories, Inc., GlaxoSmithKline, MannKind Corporation, Novartis Pharmaceuticals Corporation, Takeda Pharmaceuticals North America, Inc., and Tolerx, Inc. She is also on the speakers bureau for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Daiichi Sankyo Co., Ltd., Kowa Pharmaceuticals America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and the Sanofi-aventis US Group. Dr. Dandona is on the advisory panel for Merck & Co., Inc., and the Sanofi-aventis US Group, and is a consultant for Novo Nordisk Inc. He has received research support from Amylin Pharmaceuticals, Inc., Merck & Co., Inc., and the Sanofi-aventis US Group. He is on the speakers bureau for Amylin Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk Inc., and the Sanofi-aventis US Group. Dr. Ilgenfritz was an employee of United Biosource Corporation during the development of this manuscript. Dr. Riddle has received grant support from Amylin Pharmaceuticals, Inc., GlaxoSmithKline, Eli Lilly and Company, Sanofi-aventis US, and honoraria for consulting from Amylin Pharmaceuticals, Inc., Eli Lilly and Company, Pfizer Inc, Roche, and Sanofi-aventis US.

Author contributions

A. Chaudhuri, J. Rosenstock, A. DiGenio, L. Meneghini, P. Hollander, J. B. McGill, P. Dandona, J. Ilgenfritz, and M. Riddle analysed the data, contributed to discussions, and reviewed/edited the manuscript.

References

1. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007; 30(1): 162–172.
2. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007; 115(12): 1544–1550.
3. Grundy SM, Benjamin LI, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999; 100(10): 1134–1146.
4. Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003–2004. Am Heart J 2008; 156(1): 112–119.
5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486–2497.
6. American Diabetes Association. Standards of medical care in diabetes – 2010. Diabetes Care 2010; 33(suppl 1): S11–S61.
7. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113(19): 2363–2372.
8. Riddle MC. The underuse of insulin therapy in North America. Diabetes Metab Res Rev 2002; 18(suppl 3): S42–S49.
9. Sasali A, Leahy JL. Insulin therapy for type 2 diabetes. Curr Diab Rep 2003; 3(5): 378–385.
10. Cheng AV, Leiter LA. Cardiovascular risk and glycemic control. CMAJ 2009; 180(9): 907–908.
11. Cariou B, Fruchart JC, Staels B. Vascular protective effects of peroxisome proliferator-activated receptor agonists. Br J Diabetes Vasc Dis 2005; 5: 126–132.
12. Cranberry MC, Hawkins JB, Franks AM. Thiazolidinediones in patients with type 2 diabetes mellitus and heart failure. Am J Health Syst Pharm 2007; 64(9): 931–936.
13. Unger RH. Lipotoxic diseases. Annu Rev Med 2002; 53: 319–336.
14. Unger RH. Reinventing type 2 diabetes: pathogenesis, treatment, and prevention. JAMA 2008; 299(10): 1185–1187.
15. Gerstein HC, Yale J-F, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoid-
ance of insulin in people with type 2 di-
abetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian IN-
SIGHT (Implementing New Strategies with Insulin Glargin for Hyperglycaemia Treatment) Study. Diabet Med 2006; 23(7): 736–742.

16. Reynolds LR, Kingsley FJ, Karounos DG, Tannock FR. Differential effects of rosi-
glitazone and insulin glargine on inflam-
matory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract 2007; 77(2): 180–187.

17. Riddle MC, Schneider J. Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insu-
lin alone. Glimepiride Combination Group. Diabetes Care 1998; 21(7): 1052–1057.

18. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Dia-betologia 2004; 47(2): 442–451.

19. Rosenstock J, Sugimoto D, Strang P, Stewart JA, Soltesz-Rak E, Dailey G. Tri-
ple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to com-
bination therapy of sulfonylurea plus metformin in insulin-naïve patients. Diabetes Care 2006; 29(3): 554–559.

20. Meneghini LF, Taylor L, Schwartz S. Im-
proved glycemic control with insulin glargine vs pioglitazone as add-on ther-
apy to sulfonylurea or metformin in patients with uncontrolled type 2 dia-
betes. Endocr Pract 2010; 16(4): 588–599.

21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of serum lipids in type 2 diabetes. Taskinen MR, Amatruda JM, Grundy SM. Joint distribu-
tion of non-HDL and LDL cholesterol and coronary heart disease risk predic-
tion among individuals with and without diabetes. Diabetes Care 2005; 28(8): 1916–1921.

22. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 dia-
betes: the Strong Heart Study. Diabetes Care 2003; 26(1): 16–23.

23. Taskinen MR, Kuusi T, Taskinen MR. Persistent abnormalities in lipoprotein composition in noninsulin-
dependent diabetes after intensive insulin therapy. Arterioscler Thromb 1990; 10(2): 232–239.

24. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROActive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366(9493): 1279–1289.

25. Spanheimer R, Betteridge DJ, Tan MH, Ferrannini E, Charbonnel B. Long-term lipid effects of pioglitazone by baseline anti-hyperglycemia medication therapy and statin use from the PROActive experience (PROactive 14). Am J Cardiol 2009; 104(2): 234–239.

26. Chiouette E, Ramirez G, DeFrazeno R. A meta-analysis comparing the effect of thiazolidinedionediones on cardiovascular risk factors. Arch Intern Med 2004; 164(19): 2097–2104.

27. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28(7): 1547–1554.

28. Verges BL. Dyslipidaemia in diabetes mellitus. Review of the main lipoprotein abnormalities and their consequences on the development of atherosclerosis. Diabetes Metab 2004; 30(suppl 3): 32–40.

29. Lewis GF, Uffelman KD, Szeto LW, Steiner G. Effects of acute hyperinsuli-
naemia on VLDL triglyceride and VLDL apolipoprotein B production in normal weight and obese individuals. Diabetes 1993; 42(6): 833–842.

30. Jackson TK, Salhanick AI, Elovson J, Deichman ML, Amatruda JM. Insulin regulates apolipoprotein B turnover and phosphorylation in rat hepatocytes. J Clin Invest 1990; 86(5): 1746–1751.

31. Salhanick AI, Schwartz SI, Amatruda JM. Insulin inhibits apolipoprotein B se-
cretion in isolated human hepatocytes. Metabolism 1991; 40(3): 275–279.

32. Malmstrom R, Packard CJ, Caslake M, et al. Effects of insulin and acipimox on VLDL1 and VLDL2 as a predictor of cardiovascular disease in type 2 diabetes mellitus. The Strong Heart Study. Diabetes Care 2003; 26(1): 16–23.