Effects of Initiating Insulin and Metformin on Glycemic Control and Inflammatory Biomarkers Among Patients With Type 2 Diabetes

The LANCET Randomized Trial

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Context As diabetes is in part an inflammatory condition, the initiation of insulin and/or metformin may beneficially reduce levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP).

Objective To determine whether insulin alone or combined with metformin lowers levels of hsCRP, IL-6, and soluble tumor necrosis factor receptor 2 (sTNFr2) in patients with recent-onset type 2 diabetes mellitus.

Design, Setting, and Participants Randomized 2×2 factorial trial of open-label insulin glargine and placebo-controlled metformin in 500 adults with type 2 diabetes (median time from diagnosis, 2.0 years), suboptimal glycemic control, and elevated hsCRP levels. Patients were recruited from US office-based practices between October 2006 and December 2008.

Intervention Random allocation to 1 of 4 treatments (placebo metformin only, placebo metformin and insulin glargine, active metformin only, or active metformin and insulin glargine) with dose titration targeting fasting blood glucose less than 110 mg/dL.

Main Outcome Measures Change in hsCRP level (primary end point) and change in IL-6 and sTNFr2 levels (secondary end points) from baseline to 14 weeks.

Results Levels of glucose and glycated hemoglobin (HbA_{1c}) were significantly reduced with active treatment vs placebo (all *P* values <.001). Levels of hsCRP were reduced in all 4 groups. There was no significant difference in hsCRP reduction among those allocated to insulin (–11.8%; 95% CI, –18.7% to –4.4%) or to no insulin (–17.5%; 95% CI, –23.9% to –10.5%) (*P* for difference=.25), or among those allocated to active metformin (–18.1%; 95% CI, –24.4% to –11.1%) or placebo metformin (–11.2%; 95% CI, –18.1% to –3.7%) (*P* for difference=.17). In the individual treatment groups, despite a differential impact on glucose control, reductions in hsCRP in the metformin (–16.1%; 95% CI, –25.1% to –6.1%) and metformin plus insulin (–20.1%; 95% CI, –28.8% to –10.4%) groups were no different than reductions with placebo alone (–19.0%; 95% CI, –27.8% to –9.1%; *P*=.67 and .87 vs placebo, respectively). By contrast, hsCRP reduction was attenuated with insulin alone (–2.9%, 95% CI, –13.2% to 8.6%; *P*=.03 vs placebo). Similar findings were noted for levels of IL-6 and sTNFr2.

Conclusion In patients with recent-onset type 2 diabetes, treatment with insulin or metformin compared with placebo did not reduce inflammatory biomarker levels despite improving glucose control.

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ALTHOUGH THE BENEFITS OF AGgressive glucose control on microvascular complications in type 2 diabetes mellitus are well established, data on whether cardiovascular disease (CVD) can be prevented with intensive glucose control are conflicting. Recent findings from 3 studies[1-3] of intensive glycemic control for CVD prevention raise doubt as to whether macrovascular benefits can be achieved. All 3 trials were undertaken among patients with established diabetes (average duration, 8-11 years) and either known CVD or multiple risk factors. By contrast, a recent meta-analysis[4] of these trials and 2 others[5-7] reported a 17% reduction in nonfatal myocardial infarction and no increase in all-cause mortality. However, the study populations, drugs used for glycemic control, and duration of follow-up varied between studies. Subgroup analyses from the 3 more recent trials have suggested that risk reduction might be attained in younger patients with short duration of disease, lower levels of glycated hemoglobin (HbA_{1c}) on initiation of intensified glucose control, and absence of established CVD.[8] These latter findings have lent support for more stringent treatment goals for younger individuals with more recent diabetes onset.[8,9]

Although these results indicate that glucose lowering for CVD prevention may

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yet be beneficial in a subset of diabetic patients, they also invite consideration of alternate therapeutic targets. Subclinical inflammation is one such modifiable risk factor.[10] Proinflammatory mechanisms have been linked to the core metabolic defects of beta-cell insufficiency and insulin resistance,[11-13] and elevations in levels of inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP), IL-6, and soluble tumor necrosis factor receptor 2 (sTNFr2), predict incident type 2 diabetes among apparently healthy individuals.[14-18] These markers also predict incident myocardial infarction and stroke,[19-21] and more recent clinical trial data[22,23] have demonstrated hsCRP reduction is associated with marked improvement in vascular outcomes.

On this basis, it has been hypothesized that improvement in glycemic control, insulin resistance, or both with antidiabetic agents such as insulin and metformin may beneficially modulate inflammation.[24,25] To date, no large-scale randomized trial has directly evaluated whether the dual goals of glycemic control and amelioration of subclinical inflammation can be achieved with early aggressive diabetes management, and clinical data on potential anti-inflammatory effects of insulin have been sparse.

METHODS

Trial Design

The Lantus for C-reactive Protein Reduction in Early Treatment of Type 2 Diabetes (LANCET) trial was an investigator-initiated 2×2 factorial trial of open-label insulin glargine and placebo-controlled metformin in patients with type 2 diabetes, suboptimal glycemic control (screening HbA_{1c}, 7.0%-10.0%), and elevated levels of hsCRP (≥2.0 mg/L). All patients provided written informed consent. The study was approved by the institutional review board of the Brigham and Women's Hospital that exercised oversight for the clinical coordinating center and a central institutional review board having jurisdiction over the clinical sites.

Participants were diabetic 18- to 79-year-olds who were undergoing non-pharmacologic therapy or non-metformin monotherapy with a sulfonylurea or thiazolidinedione. Recruitment occurred at 73 US office-based practices between October 2006 and December 2008. Pre-enrollment evaluation comprised local laboratory testing of hsCRP, HbA_{1c}, and safety parameters (alanine aminotransferase or aspartate aminotransferase and creatinine). Eligible participants were enrolled in a 2-week run-in during which the ability to self-monitor fingerstick blood glucose and perform insulin injection was determined and evaluation for evidence of marked hyperglycemia was undertaken.

Major exclusion criteria were established type 1 diabetes or positive anti–glutamic acid decarboxylase antibody; baseline use of metformin, insulin, or monotherapy with antidiabetic agents other than a sulfonylurea or thiazolidinedione; evidence of marked hyperglycemia during the run-in period (fasting self-monitored blood glucose [SMBG] ≥250 mg/dL confirmed with plasma-based testing, or any SMBG ≥400 mg/dL; to convert to mmol/L, multiply by 0.0555); pregnancy; lactation; intention to become pregnant during the course of the study; history of congestive heart failure requiring pharmacologic therapy; active liver or kidney disease; recent (<3 months) initiation or change in dose of statins, fibric acid derivatives, angiotensin-receptor blockers, or nonsteroidal anti-inflammatory medications; an acute infectious process; recent surgery; or trauma occurring within the month prior to enrollment.

The primary study aims were to evaluate whether insulin glargine is associated with a difference in hsCRP reduction compared with no insulin (main effect of insulin) and to evaluate whether insulin glargine added to metformin was associated with a difference in hsCRP reduction compared with metformin alone (subgroup effect). Allocation to insulin was anticipated to be associated with greater decreases in hsCRP level. Consistent with a 2×2 factorial design, secondary aims were to evaluate the main effect of metformin and to compare hsCRP reduction among the 4 individual treatment groups. On a prespecified basis, differential effects on the levels of 2 alternative inflammatory biomarkers, IL-6 and sTNFr2, were also evaluated.

Interventions and Clinical Follow-up

Allocation to metformin or placebo pill was double-blinded. Randomization was stratified by prestudy treatment with lifestyle management only, use of a sulfonylurea, or use of a thiazolidinedione and performed using computer-generated permuted blocks of 8 in strata defined by prestudy treatment. The random allocation sequence was implemented by telephone call to the clinical coordinating center, and treatment allocation was concealed until the intervention was assigned.

Participants were assigned at random to active metformin or placebo metformin and then within each of these categories to open-label bedtime insulin glargine or to no insulin. Diet and exercise advice was provided to all participants in the form of a patient- and clinician-friendly diabetes education handout that incorporated current, evidence-based recommendations that were reinforced at each study visit. All participants were provided glucose monitoring devices (Accu-Chek Advantage; Roche Diagnostics; Indianapolis, Indiana) and instructed on their appropriate calibration and use for the course of the trial.

Drug titration occurred according to the median of 3-day fasting SMBG values from glucose diaries to a target of less than 110 mg/dL. Insulin glargine was started at a fixed bedtime dose (5 U). Metformin was formulated as 500-mg metformin hydrochloride with placebo pills matched for size and appearance. For participants assigned to combination groups, the initial pill dose was 1 pill at dinner with weekly titration by 1 pill to a maximum of 4 pills per day. Insulin titration occurred on the fourth day and weekly thereafter throughout the course of the trial. For participants assigned to pills only, the

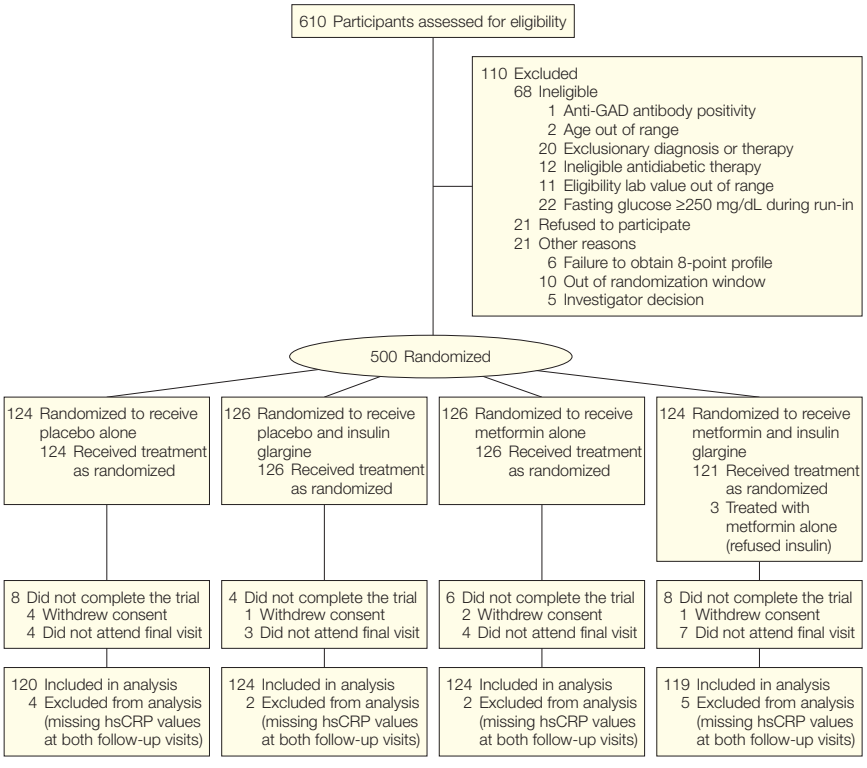
initial pill dose was 1 pill twice daily titrated to a maximum 2 pills twice daily. In the event of significant hypoglycemia (SMBG <70 mg/dL), interventions were sequentially back-titrated. The dose of baseline oral monotherapy was maintained at prerandomization levels throughout the duration of the trial.

Participants were contacted by a study nurse every 3 days during the first 2 weeks and at the discretion of the study nurse or physician thereafter. Study visits occurred in the clinic at 2-, 6-, and 14-week (end-of-study) time points. During clinic visits, glucose diaries including a 1-day 8-point profile were reviewed, weight was measured, and assessments were made for adherence and adverse events. Participants were contacted at 10 weeks by telephone to review glucose diaries and monitor for adverse events. All SMBG data used for dose titration and immediately prior to routine study visits were centrally collected, reviewed for protocol adherence, and entered into the database. Fasting blood specimens were collected at enrollment, randomization, and 6- and 14-week follow-up.

Outcomes

The primary end point was change in hsCRP level from baseline to 14 weeks. As the distribution of hsCRP is skewed, on a prespecified basis hsCRP levels were transformed to a natural log scale (lnCRP) for statistical considerations. The change in lnCRP, which is equivalent to the percentage change in original units, was calculated and compared between treatment groups. Prespecified secondary end points included change in long-term glycemic control as measured by HbA_{1c} level, change in IL-6 and sTNFr2 levels, change in weight (≥5% of baseline weight), and occurrence of marked hypoglycemia (blood glucose <56 mg/dL necessitating third-party assistance or recovery with presumptive therapy).

Figure 1. Study Flow Diagram



Numbers included in analysis had high-sensitivity C-reactive protein (hsCRP) measured at the 6-week and 14-week follow-up. GAD indicates glutamic acid decarboxylase.

Laboratory Analysis

High-sensitivity CRP was determined using an immunoturbidimetric assay with reagents and calibrators from DiaSorin (Stillwater, Minnesota). The day-to-day variability of the assay at concentrations of 0.91, 3.07, and 13.38 mg/L were 2.81%, 1.61%, and 1.1%, respectively. HbA_{1c} was estimated using turbidimetric immunoinhibition on packed red blood cells. The day-to-day variability at % HbA_{1c} values of 5.5 and 9.1 were 1.9% and 3.0%, respectively. Both hsCRP and HbA_{1c} were measured on the Hitachi 917 analyzer (Roche Diagnostics). IL-6 and sTNFr2 were measured by assays from R&D Systems (Minneapolis, Minnesota). The interassay coefficients of variation for these latter biomarkers using 3 levels of control materials ranged from 3.5% to 9.6%. All blood glucose measurements were performed on capillary blood using glucometers from a single manufacturer (Accu-Chek Advantage).

Statistical Analysis

To reduce measurement error, the baseline hsCRP value was calculated as the mean of lnCRP values obtained at the enrollment and randomization visits. As hsCRP was also measured at both 6 and 14 weeks, linear mixed models conditioning on baseline hsCRP and adjusting for treatment stratum were constructed with the dependent variable being change in lnCRP. The means at each time point were estimated from a repeated-measures model incorporating all 3 time points. The interventions were assessed by fitting terms corresponding to study drug assignment. Adjusted models included terms for baseline HbA_{1c} and weight and change in weight at each time point.

The presence of interaction between treatments was determined by including an interaction term in the regression model. To facilitate comparison of change in hsCRP with changes in other key variables, including glycemic control and

weight, these latter variables were considered for natural log transformation. All were log-normal and changes in these variables were modeled using the same analytic approach as for the main outcome, change in hsCRP. As IL-6 and sTNFr2 levels were only determined at baseline and 14 weeks, results derive from linear regression models that adjusted for the baseline measure. All regression models were adjusted for baseline treatment stratum. The comparisons of adverse events used Fisher exact testing for main effects of the study drugs on these outcomes. All *P* values were unadjusted for multiple comparisons. All testing was 2-tailed at the .05 significance level. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Sample Size and Interim Analyses

To cover a broad range of potential outcomes, a highly conservative sample size of 800 was selected. This allowed adequate power to detect a clinically important main effect for glargine insulin of 20% hsCRP reduction if metformin had as much as a 30% independent effect. This projected sample size also included considerations for a 10% dropout rate and an assumed 90% adherence rate among completers of the trial.

For safety, efficacy, and cost considerations, a prespecified blinded interim analysis was performed by the data and safety monitoring board when 360 participants had completed the trial. The primary purpose of this in-

Table 1. Baseline Characteristics of the Study Population

Characteristics	Placebo Alone (n = 124)	Placebo and Insulin Glargine (n = 126)	Metformin Alone (n = 126)	Metformin and Insulin Glargine (n = 124)	*P* Value[a]	Total/Overall (n = 500)
Age, mean (SD), y	54.0 (10.9)	53.8 (11.4)	53.8 (11.5)	54.0 (11.7)	>.99	53.9 (11.4)
Women, No. (%)	64 (51.6)	83 (65.9)	68 (54.0)	66 (53.2)	.09	281 (56.2)
Race, No. (%)						
White	91 (73.4)	95 (75.4)	88 (69.8)	91 (73.4)	.56	365 (73.0)
African American	25 (20.2)	25 (19.8)	34 (27.0)	24 (19.4)		108 (21.6)
Other	8 (6.4)	6 (4.8)	4 (3.2)	9 (7.3)		27 (5.4)
Hispanic/Latino, No. (%)						
Yes	13 (10.5)	19 (15.1)	4 (3.2)	17 (13.7)	.05	53 (10.6)
No	110 (88.7)	104 (82.5)	119 (94.4)	105 (84.7)		438 (87.6)
Not reported	1 (0.8)	3 (2.4)	3 (2.4)	2 (1.6)		9 (1.8)
Weight, mean (SD), lb	236.3 (60.3)	223.0 (47.5)	229.4 (53.2)	224.1 (50.3)	.18	228.2 (53.1)
BMI, mean (SD)[b]	37.2 (8.2)	36.4 (7.1)	36.2 (8.1)	35.6 (7.9)	.48	36.4 (7.8)
<25.0, No. (%)	3 (2.4)	2 (1.6)	6 (4.8)	5 (4.0)		16 (3.2)
25.0-29.9, No. (%)	16 (12.9)	19 (15.2)	22 (17.6)	25 (20.2)		82 (16.5)
>30.0, No. (%)	105 (84.7)	104 (83.2)	97 (77.0)	94 (75.8)		400 (80.3)
Diagnosed hypertension, No. (%)	84 (67.7)	79 (62.7)	88 (69.8)	90 (72.6)	.41	341 (68.4)
Diagnosed hyperlipidemia, No. (%)	71 (57.3)	75 (59.5)	71 (56.3)	82 (66.1)	.39	299 (59.8)
Current smoking, No. (%)	25 (20.2)	27 (21.6)	24 (19.0)	24 (19.4)	.96	100 (20.0)
Cardiovascular disease, No. (%)	9 (7.3)	14 (11.1)	10 (7.9)	10 (8.1)	.70	43 (8.6)
Aspirin, No. (%)	46 (37.1)	48 (38.1)	42 (33.3)	45 (36.3)	.88	181 (36.2)
Statins, No. (%)	53 (42.7)	47 (37.3)	48 (38.1)	55 (44.4)	.60	203 (40.6)
Fibric acid derivatives, No. (%)	8 (6.5)	7 (5.6)	11 (8.7)	10 (8.1)	.75	36 (7.2)
Any lipid-modifying agent, No. (%)	58 (46.8)	52 (41.3)	54 (42.9)	61 (49.2)	.58	225 (45.0)
ACE-I or ARB, No. (%)	70 (56.5)	61 (48.4)	66 (52.4)	69 (55.7)	.57	266 (53.2)
NSAID, No. (%)	26 (21.0)	20 (15.9)	28 (22.2)	15 (12.1)	.13	89 (17.8)
Baseline diabetes treatment, No. (%)						
Nonpharmacologic	67 (54.0)	67 (53.2)	65 (51.6)	68 (54.8)	>.99	267 (53.4)
Thiazolidinedione	17 (13.7)	18 (14.3)	20 (15.9)	18 (14.5)		73 (14.6)
Sulfonylurea	40 (32.3)	41 (32.5)	41 (32.5)	38 (30.6)		160 (32.0)
Time since diabetes diagnosis, median (IQR), y	1.6 (0.2-5.0)	2.7 (0.4-5.7)	1.2 (0.2-6.2)	2.0 (0.3-5.3)	0.25	2.0 (0.2-5.6)
HbA_{1c}, median (IQR), %	6.9 (6.4-8.0)	6.9 (6.3-7.5)	6.7 (6.3-7.4)	7.1 (6.4-7.9)	.03	6.9 (6.3-7.7)
Geometric mean (95% CI)	7.2 (7.0-7.3)	7.0 (6.9-7.2)	6.8 (6.7-7.0)	7.1 (7.0-7.3)	.04	7.0 (7.0-7.1)
Fasting SMBG, median (IQR), mg/dL	169 (143-194)	161 (138-191)	165 (143-188)	168 (147-194)	.59	165 (143-192)
Geometric mean (95% CI)	168 (161-175)	160 (154-167)	163 (156-170)	165 (158-172)	.44	164 (161-168)
2-h postprandial SMBG, median (IQR), mg/dL	194 (163-234)	191 (166-217)	195 (166-217)	196 (164-238)	.67	195 (165-227)
Geometric mean (95% CI)	194 (186-203)	191 (182-199)	191 (183-200)	196 (188-205)	.76	193 (189-197)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CI, confidence interval; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SMBG, self-monitored blood glucose.
SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.
[a] *P* values for any difference in groups derived from the χ^2 test for categorical variables, analysis of variance for means, or Kruskal-Wallis for median values.
[b] Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.

terim analysis was to determine whether to continue to a planned full enrollment of 800 participants or to stop further enrollment because of evidence of strong effectiveness or futility. Futility was defined as the inability to detect a reduction of at least 15% for the main effect of insulin. To determine probable effectiveness or futility, a prespecified cut point of 15% was chosen so the chance of early enrollment curtailment could be controlled to be no more than 0.05 if the population mean was in fact 15%. The *P* value for the final test at the conclusion of the study was not modified by this interim analysis.

On December 1, 2008, the data and safety monitoring board reviewed the interim data and recommended enrollment curtailment due to evidence of futility. All participants enrolled at this time were allowed to complete the study and comprise the cohort used in these analyses (n=500). To address the issue of potential bias related to early termination of the trial, data from the 360 participants who were included in the interim analysis were qualitatively compared with results in the total study population.

RESULTS

Between October 2006 and December 2008, 610 participants entered the run-in and were screened for eligibility, of whom 500 (82.0%) underwent randomization (FIGURE 1). Baseline characteristics of participants are provided in TABLE 1.

Change in Glucose and HbA_{1c} Levels and Weight

Glucose and HbA_{1c} levels were significantly reduced with active treatment compared with placebo (all *P* values <.001) with the greatest reductions in all glycemic parameters among those allocated to combination therapy (FIGURE 2). HbA_{1c} level was near normalized in the active treatment groups. All study groups except those allocated to insulin alone experienced a modest decline in weight; the mean weight change (% change) from baseline was −3.2 lbs (−1.4%) for placebo alone, −4.1 lb (−1.9%) for metformin alone, and −1.6 lb (−0.7%) for metformin and insulin (all $P<.04$ vs baseline, and both *P* values nonsignificant for active groups vs placebo alone [metformin vs placebo alone, $P=.29$; metformin and insulin vs placebo alone, $P=.17$]) while allocation to insulin and placebo metformin was associated with a nonsignificant 0.5-lb weight gain (+0.2%; $P=.47$ vs baseline; $P=.001$ vs placebo alone). The median end-of-study insulin dose was 0.4 U/kg (interquartile range, 0.2-0.5 U/kg) for those allocated to metformin and 0.5 U/kg (interquartile range, 0.3-0.7 U/kg) for those allocated to metformin placebo. The vast majority of participants (91.6%) were taking the maximum dose of metformin or metformin placebo (2 pills twice daily) at the final visit.

Treatment Effects on hsCRP Level

TABLE 2 shows the main effects of insulin glargine and metformin on hsCRP level as well as effects within each of the 4 individual treatment groups. Estimates are derived from a basic model adjusted for treatment stratum and conditioned on baseline hsCRP level, and expanded multivariable models additionally adjusted for baseline HbA_{1c} level, weight, and change in weight at each time point.

Levels of hsCRP were reduced from baseline in all 4 study groups. In analyses of main effects, there was no significant difference in hsCRP reduction among those allocated to insulin as compared with no insulin ($P=.25$) or among those allocated to metformin as compared with no metformin ($P=.17$). An interaction ($P=.048$) between interventions was observed and was most evident in comparisons of subgroup effects. The addition of insulin to placebo metformin was associated with attenuation of hsCRP reduction; −2.9% for insulin and placebo metformin vs −19.0% for placebo alone ($P=.03$ for difference in effects). This effect was not observed when insulin was added to active metformin: −20.1% for insulin and metformin vs −16.1% for metformin alone; $P=.55$). Despite a gradient in achieved glycemic control, no active treatment group demonstrated incremental benefit on decrease in hsCRP level compared with placebo alone (Table 2). Adjustment for baseline HbA_{1c} level and weight and change in weight at each time point had no impact on these results. In sensitivity analyses (eTable available at http://www.jama.com), there were no qualitative differences according to baseline treatment stratum or when individuals who had altered baseline antidiabetic therapy or statin medications (n=33) were excluded from the analysis. Effects of the study treatments on IL-6 and sTNFr2 levels paralleled those for hsCRP level (FIGURE 3).

Sensitivity Analyses

Thirteen participants (2.6%) were not included in the main analysis because of missing hsCRP values at both follow-up visits. In sensitivity analyses using imputed data from randomly selected participants in the placebo group, results were nearly identical. There was no significant treatment effect of either insulin ($P=.25$ vs no insulin) or metformin ($P=.11$ vs no metformin), with a persistent interaction between treatments ($P=.03$). As to the possibility of bias related to early termination of the trial, estimates of the main effects and effects in individual treatment groups were similar in the interim analysis population as in the total study population. Further, in a post hoc subgroup analysis limited to those completing the trial after the interim analysis decision to curtail enrollment, there was no significant decrease in hsCRP level among those allocated to insulin vs no insulin ($P=.29$) or to metformin vs no metformin ($P=.48$).

Adherence and Safety

Adherence was determined by self-report at clinic visits. Pill adherence, defined as taking at least 80% of pills, was 98.1% overall, and there was no difference between adherence comparing active metformin with placebo metformin in the total population ($P>.99$) or within the subgroup treated in combination with open-label insulin glargine ($P=.62$). Adherence with insulin (no missed injections) was 87.7%. Excluding participants

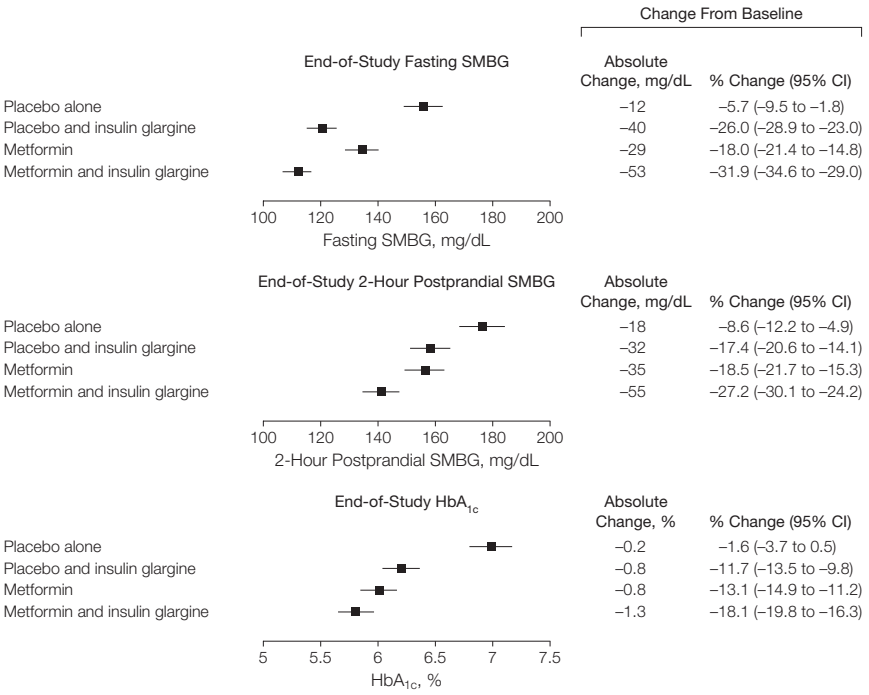
lost to follow-up, 6 participants permanently discontinued medications, with no difference between individual treatment groups ($P=.95$).

Severe hypoglycemia was more common among those allocated to combination therapy (n=6) and confirmed hyperglycemia more common among those allocated to no pharmacologic intervention (n=10). One participant in the placebo alone group developed hyperglycemia requiring hospitalization and treatment with nonstudy insulin. In formal comparisons of main effects, reports of serious adverse events not related to hyperglycemia or hypoglycemia were lower among those allocated to insulin glargine as compared with the no insulin groups (2 vs 11, $P=.01$) and similar among those allocated to metformin or no metformin (8 vs 5, $P=.40$). Weight gain of 5% or more of baseline was more common among those allocated to insulin compared with no insulin (22 vs 7, $P=.01$) and not significantly different among those allocated to metformin compared with no metformin (12 vs 17, $P=.35$). Gastrointestinal adverse effects were more common among those allocated to metformin as compared with no metformin (21 vs 7, $P=.01$) (TABLE 3).

COMMENT

In this randomized 2 × 2 factorial trial of insulin glargine and metformin initiation, no consistent association was found between glucose reduction and improvement in inflammatory status as ascertained by change in levels of hsCRP, IL-6, or sTNFr2. Despite sub-

Figure 2. Impact of Individual Treatments on Levels of Glucose, HbA_{1c}, and Weight



End-of-study geometric mean levels of fasting self-monitored blood glucose (SMBG), 2-hour postprandial SMBG, and glycated hemoglobin (HbA_{1c}) are plotted for each of the 4 individual treatment groups. Models were adjusted for treatment stratum and conditioned on baseline values. All P values <.001 for comparisons vs placebo. Error bars indicate 95% confidence intervals (CIs).

Table 2. Effects of Study Medications on hsCRP Level: Main Effects and Individual Treatment Groups

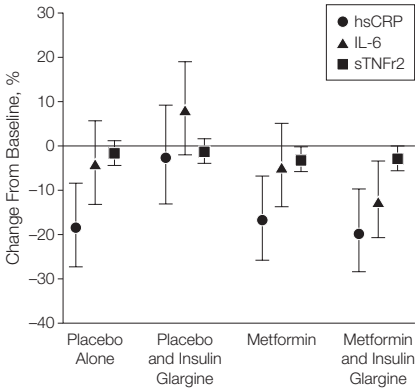
Intervention	Participants, No.	Baseline hsCRP Geometric Mean (95% CI)	End of Study: Achieved hsCRP Geometric Mean (95% CI)	End of Study: % Change From Baseline (95% CI)[a]	End of Study: *P* Value[b]	End of Study: Adjusted % Change From Baseline (95% CI)[c]	End of Study: *P* Value[b]
Main effects							
No insulin glargine	244	4.5 (4.0 to 5.1)	3.7 (3.2 to 4.2)	–17.5 (–23.9 to –10.5)	.25	–17.3 (23.8 to –10.3)	.26
Insulin glargine	243	4.2 (3.7 to 4.8)	3.7 (3.3 to 4.3)	–11.8 (–18.7 to –4.4)		–11.6 (–18.5 to –4.1)	
No metformin	244	4.5 (4.0 to 5.1)	4.0 (3.5 to 4.6)	–11.2 (–18.1 to –3.7)	.17	–10.8 (–17.8 to –3.3)	.15
Metformin	243	4.2 (3.7 to 4.8)	3.5 (3.0 to 4.0)	–18.1 (–24.4 to –11.1)		–18.1 (–24.5 to –11.1)	
Individual groups							
Placebo alone	120	4.7 (3.9 to 5.6)	3.8 (3.1 to 4.6)	–19.0 (–27.8 to –9.1)		–18.4 (–27.3 to –8.3)	
Placebo and insulin glargine	124	4.3 (3.7 to 5.2)	4.2 (3.5 to 5.1)	–2.9 (–13.2 to 8.6)	.03	–2.8 (–13.3 to 8.9)	.04
Metformin alone	124	4.3 (3.6 to 5.1)	3.6 (3.0 to 4.4)	–16.1 (–25.1 to –6.1)	.67	–16.5 (–25.6 to –6.4)	.79
Metformin and insulin glargine[d]	119	4.1 (3.4 to 4.9)	3.3 (2.7 to 4.0)	–20.1 (–28.8 to –10.4)	.87	–19.7 (–28.5 to –9.9)	.84

Abbreviations: CI, confidence interval; hsCRP, high-sensitivity C-reactive protein.
[a] Adjusted for baseline treatment stratum, conditioned on baseline hsCRP.
[b] *P* value for comparison with no intervention or placebo as appropriate.
[c] Additionally adjusted for baseline glycated hemoglobin level, weight, and change in weight at each time point.
[d] *P* value for the prespecified comparison of those allocated to metformin and insulin with metformin alone=.55.

stantially improving glucose control, neither insulin nor metformin reduced inflammatory biomarker levels for the main effects evaluated or in comparisons between the individual treatment groups. An interaction between interventions was observed such that, compared with no pharmacologic intervention, those allocated to insulin alone had a significant attenuation of inflammation reduction, an effect not observed among those allocated to metformin and insulin or to metformin alone.

These data may be helpful in understanding results of 3 recent, large cardiovascular outcome trials conducted among patients with type 2 diabetes[1-3] in which intensive glycemic control failed to lower the risk of incident CVD. These results are puzzling in light of strong epidemiologic evidence of a graded association between hyperglycemia and future vascular events. In this context, the current finding that improvement in inflammatory status did not occur despite improvement in glycemic control offers one potential explanation for a lack of clinical benefit. The heterogeneity of treatment effects on insulin initiation alludes to another, as the choice of antidiabetic agent and drug combinations may play a contributing role.

Figure 3. Impact of Individual Treatments on Inflammatory Biomarkers



Models are adjusted for treatment stratum and baseline biomarker levels. hsCRP indicates high-sensitivity C-reactive protein; sTNFr2, soluble tumor necrosis factor receptor 2. Error bars indicate 95% confidence intervals.

Allocation to placebo was associated with a 19% reduction in hsCRP over the 14-week period, an effect that may in part reflect lingering regression to the mean due to the study design, but may also reflect a mean weight loss of 3.2 lb (−1.4%) as a result of adherence to diet and exercise advice. A comparable change in weight was also observed among those treated with metformin and insulin and metformin alone. In contrast, compared with placebo those treated with insulin alone did not achieve a similar degree of weight loss. Although adjustment for weight change did not alter the findings, the mechanisms of weight change as they relate to visceral vs subcutaneous adiposity may have differed across individual treatment groups. In the Diabetes Prevention Program (DPP),[26] intensive lifestyle modification was associated with a marked decline in visceral adipose tissue while treatment with metformin reduced subcutaneous fat but had minimal impact on visceral adiposity. In contrast, insulin initiation in type 2 diabetes has been associated with increased central obesity,[27] although data in this regard are sparse. Because visceral fat is closely linked with subclinical inflammation,[28] the mechanisms of treatment associated weight change and change in body fat distribution may be important areas for further investigation.

Prior data pertaining to hsCRP reduction with insulin in type 2 diabetes are limited. The current findings are consistent with small studies[29-31] in which insulin initiation, whether with lispro insulin infusion, insulin glargine injection, or NPH insulin injection, was not associated with demonstrable improvement in hsCRP levels. If anything, hsCRP increases of variable statistical significance were noted despite marked improvements in HbA_{1c} levels. However, adjustment for baseline differences in biomarker levels and weight change were not uniformly performed. In 1 recent study[32] of 90 Chinese adults with newly diagnosed diabetes, insulin appeared to have a greater impact than metformin on hsCRP and IL-6 reduction after 8 weeks of treatment. However, hsCRP and IL-6 levels decreased in both treatment groups and a placebo comparator was not included. More robust data derive from a secondary analysis of the Diabetes Control and Complications Trial,[33] in which a significant increase in both hsCRP and TNF levels was observed with intensive vs conventional insulin therapy. Although the increase in hsCRP level was related to weight gained during the 3-year follow-up, changes in TNF level were not.

CRP reduction with metformin has been more widely evaluated. Most but not all[34,35] studies demonstrate hsCRP lowering with a broad range of short-

Table 3. Occurrence of Adverse Events

Variable	No. (%)			
	Placebo Alone (n = 124)	Placebo and Insulin Glargine (n = 126)	Metformin Alone (n = 126)	Metformin and Insulin Glargine (n = 124)
Serious adverse event	3 (2.4)	2 (1.6)	8 (6.3)	0
Related[a]	1 (0.8)	0	2 (1.6)	0
Severe hypoglycemia	1 (0.8)	3 (2.4)	3 (2.4)	6 (4.8)
Hyperglycemia				
Confirmed fasting glucose ≥250 mg/dL	10 (8.1)	4 (3.2)	1 (0.8)	1 (0.8)
Any SMBG ≥400 mg/dL	3 (2.4)	3 (2.4)	0	1 (0.8)
Weight gain (≥5% of baseline)	3 (2.4)	14 (11.1)	4 (3.2)	8 (6.5)
Gastrointestinal adverse effect	3 (2.4)	4 (3.2)	13 (10.3)	8 (6.5)

Abbreviation: SMBG, self-monitored blood glucose.
SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.
[a]Related serious adverse events were, for metformin alone, 1 case of severe diarrhea and 1 case of supraventricular tachycardia; and for placebo alone, 1 case of hyperglycemia requiring hospitalization.

term effects. Unfortunately, inclusion of a placebo group was infrequent as was adjustment for weight change. In the DPP, by far the largest study to date,[36] metformin was associated with modest (–7% for men, –14% for women) but significant changes in hsCRP level at 1 year of follow-up in nondiabetic patients with glucose intolerance. Participants allocated to intensive lifestyle intervention achieved the greatest benefit (–33% for men and –29% for women). The current data regarding metformin demonstrate no significant treatment effect, but also no hazard compared with placebo as patients in both treatment groups achieved about a 20% decrease in hsCRP level.

Several potential limitations of this study merit consideration. First, this trial evaluated the effects of interventions on several surrogate markers of CVD risk. As such, the data pertaining to 14-week treatment effects on hsCRP, IL-6, and sTNFr2 levels cannot be equated with long-term effects on cardiovascular events. Indeed, 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS)[37] cohort suggests that the potential benefits of glycemic control early in type 2 diabetes may emerge after the period of intensive therapy. Second, weight change could not be distinguished as it relates to change in visceral fat. Finally, because LANCET participants were young and obese and had a lower prevalence of cardiovascular disease and relatively low baseline HbA_{1c}, these data may not be generalizable to all individuals with type 2 diabetes. However, the data do pertain to diabetic patients currently being considered for more aggressive glucose lowering for CVD prevention. Importantly, these data in stable outpatients may also not pertain to the potential anti-inflammatory effects of insulin in acute coronary syndromes or other critically ill patients.[38]

In conclusion, despite substantially improving glucose control, neither insulin nor metformin improved inflammatory status among individuals with type 2 diabetes initiating therapy. From a pathophysiologic perspective, these data provide insights into the complex interrelationships that underlie inflammation and atherosclerosis in diabetic patients. From a clinical perspective, until other endpoint trial data become available,[39] these data underscore the need to improve adherence with therapies that do reduce cardiovascular events among diabetic patients, including exercise; weight management; smoking cessation; blood pressure control; and, in appropriate patients, antiplatelet and statin therapy.

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REFERENCES

1. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.

2. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.

3. Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139.

4. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus. *Lancet*. 2009;373(9677):1765-1772.

5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.

6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352 (9131):854-865.

7. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. *Lancet*. 2005;366(9493): 1279-1289.

8. American Diabetes Association. Standards of medical care in diabetes: 2009. *Diabetes Care*. 2009; 32(suppl 1):S13-S61.

9. Kahn SE. Glucose control in type 2 diabetes. *JAMA*. 2009;301(15):1590-1592.

10. Hayden JM, Reaven PD. Cardiovascular disease in diabetes mellitus type 2. *Curr Opin Lipidol*. 2000; 11(5):519-528.

11. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia*. 1998;41(10):1241-1248.

12. Donath MY, Storling J, Maedler K, Mandrup-Poulsen T. Inflammatory mediators and islet beta-cell failure. *J Mol Med*. 2003;81(8):455-470.

13. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116(7):1793-1801.

14. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001; 286(3):327-334.

15. Barzilay JI, Abraham L, Heckbert SR, et al. The relation of markers of inflammation to the development of glucose disorders in the elderly. *Diabetes*. 2001; 50(10):2384-2389.

16. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM; Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes. *Diabetes*. 2002;51(4):1131-1137.

17. Freeman DJ, Norrie J, Caslake MJ, et al; West of Scotland Coronary Prevention Study. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes*. 2002;51(5):1596-1600.

18. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53(3):693-700.

19. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336(14):973-979.

20. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342(12):836-843.

21. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347 (20):1557-1565.

22. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.

23. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin. *Lancet*. 2009;373 (9670):1175-1182.

24. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Insulin as an anti-inflammatory and antiatherogenic modulator. *J Am Coll Cardiol*. 2009;53(5) (suppl):S14-S20.

25. Chu NV, Kong AP, Kim DD, et al. Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care*. 2002;25(3):542-549.

26. Fujimoto WY, Jablonski KA, Bray GA, et al; Diabetes Prevention Program Research Group. Body size and shape changes and the risk of diabetes in the diabetes prevention program. *Diabetes*. 2007;56(6): 1680-1685.

27. Sinha A, Formica C, Tsalamandris C, et al. Effects of insulin on body composition in patients with insulin-dependent and non–insulin-dependent diabetes. *Diabet Med*. 1996;13(1):40-46.

28. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity. *Hypertension*. 2009;53(4): 577-584.

29. Fonseca VA, Theuma P, Mudaliar S, Leissinger CA, Clejan S, Henry RR. Diabetes treatments have differential effects on nontraditional cardiovascular risk factors. *J Diabetes Complications*. 2006;20 (1):14-20.

30. Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR. Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. *Diabetes Res Clin Pract*. 2007;77(2):180-187.

31. Aas AM, Seljeflot I, Torjesen PA, Diep LM, Thorsby PM, Birkeland KI. Blood glucose lowering by means of lifestyle intervention has different effects on adipokines as compared with insulin treatment in subjects with type 2 diabetes. *Diabetologia*. 2006; 49(5):872-880.

32. Mao XM, Liu H, Tao XJ, Yin GP, Li Q, Wang SK. Independent anti-inflammatory effect of insulin in newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev*. 2009;25(5):435-441.

33. Schaumberg DA, Glynn RJ, Jenkins AJ, et al. Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the diabetes control and complications trial. *Circulation*. 2005; 111(19):2446-2453.

34. Caballero AE, Delgado A, Aguilar-Salinas CA, et al. The differential effects of metformin on markers of endothelial activation and inflammation in subjects with impaired glucose tolerance. *J Clin Endocrinol Metab*. 2004;89(8):3943-3948.

35. De Jager J, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus. *J Intern Med*. 2005;257(1): 100-109.

36. Haffner S, Temprosa M, Crandall J, et al; Diabetes Prevention Program Research Group. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes*. 2005;54(5):1566-1572.

37. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359 (15):1577-1589.

38. Nesto RW, Lago RM. Glucose: a biomarker in acute myocardial infarction ready for prime time? *Circulation*. 2008;117(8):990-992.

39. Origin Trial Investigators; Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia. *Am Heart J*. 2008;155(1):26-32, 32 e1-6.

