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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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 glycermic 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.\(^8\)\(^-\)\(^9\) 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 be beneficial, the initiation of insulin and/or metformin may also reduce levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP).

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\(^\times\)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.

Trial Registration

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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. 

Proinflammatory mechanisms have been linked to the core metabolic defects of beta-cell insufficiency and insulin resistance, 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. These markers also predict incident myocardial infarction and stroke, and more recent clinical trial data 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. 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 HbA1c, 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 nonpharmacologic 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, HbA1c, 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 pre-randomization 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 HbA1c 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).

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. HbA1c was estimated using turbidimetric immuno-inhibition on packed red blood cells. The day-to-day variability at % HbA1c values of 5.5 and 9.1 were 1.9% and 3.0%, respectively. Both hsCRP and HbA1c 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 HbA1c 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
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo Alone (n = 124)</th>
<th>Placebo and Insulin Glargine (n = 126)</th>
<th>Metformin Alone (n = 126)</th>
<th>Metformin and Insulin Glargine (n = 124)</th>
<th>P Valuea</th>
<th>Total/Overall (n = 500)</th>
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<tr>
<td>Age, mean (SD), y</td>
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<td>53.8 (11.4)</td>
<td>53.8 (11.5)</td>
<td>54.0 (11.7)</td>
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<td>53.9 (11.4)</td>
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<td>Women, No. (%)</td>
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<td></td>
<td></td>
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<td>19 (15.1)</td>
<td>4 (3.2)</td>
<td>17 (13.7)</td>
<td>.05</td>
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<td>No</td>
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<td>104 (82.5)</td>
<td>119 (94.4)</td>
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<td>438 (87.6)</td>
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<td>BMI, mean (SD)b</td>
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<td>36.4 (7.9)</td>
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<td>&lt;25.0, No. (%)</td>
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<td>25.0-29.9, No. (%)</td>
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<td>19 (15.2)</td>
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<td>82 (16.5)</td>
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<td>&gt;30.0, No. (%)</td>
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<td>104 (83.2)</td>
<td>97 (77.0)</td>
<td>94 (75.8)</td>
<td></td>
<td>400 (80.3)</td>
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<td>Diagnosed hypertension, No. (%)</td>
<td>84 (67.7)</td>
<td>79 (62.7)</td>
<td>88 (69.8)</td>
<td>90 (72.6)</td>
<td>.41</td>
<td>341 (68.4)</td>
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<td>Diagnosed hyperlipidemia, No. (%)</td>
<td>71 (57.3)</td>
<td>75 (59.5)</td>
<td>71 (56.3)</td>
<td>82 (66.1)</td>
<td>.39</td>
<td>299 (59.8)</td>
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<tr>
<td>Current smoking, No. (%)</td>
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<td>27 (21.6)</td>
<td>24 (19.0)</td>
<td>24 (19.4)</td>
<td>.96</td>
<td>100 (20.0)</td>
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<td>9 (7.3)</td>
<td>14 (11.1)</td>
<td>10 (7.9)</td>
<td>10 (8.1)</td>
<td>.70</td>
<td>43 (8.8)</td>
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<tr>
<td>Aspirin, No. (%)</td>
<td>46 (37.1)</td>
<td>48 (38.1)</td>
<td>42 (33.3)</td>
<td>45 (36.3)</td>
<td>.88</td>
<td>181 (36.2)</td>
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<td>Statins, No. (%)</td>
<td>53 (42.7)</td>
<td>47 (37.3)</td>
<td>48 (38.1)</td>
<td>55 (44.4)</td>
<td>.60</td>
<td>203 (40.6)</td>
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<td>Fibrin acid derivatives, No. (%)</td>
<td>8 (6.5)</td>
<td>7 (5.6)</td>
<td>11 (8.7)</td>
<td>10 (8.1)</td>
<td>.75</td>
<td>36 (7.2)</td>
</tr>
<tr>
<td>Any lipid-modifying agent, No. (%)</td>
<td>58 (46.8)</td>
<td>52 (41.3)</td>
<td>54 (42.9)</td>
<td>61 (49.2)</td>
<td>.58</td>
<td>225 (45.0)</td>
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<tr>
<td>ACE-I or ARB, No. (%)</td>
<td>70 (56.5)</td>
<td>61 (48.4)</td>
<td>66 (52.4)</td>
<td>69 (55.7)</td>
<td>.57</td>
<td>266 (53.2)</td>
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<td>NSAID, No. (%)</td>
<td>26 (21.0)</td>
<td>20 (15.9)</td>
<td>28 (22.2)</td>
<td>15 (12.1)</td>
<td>.13</td>
<td>89 (17.8)</td>
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<td>Baseline diabetes treatment, No. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nonpharmacologic</td>
<td>67 (54.0)</td>
<td>67 (53.2)</td>
<td>65 (51.6)</td>
<td>68 (54.8)</td>
<td>.99</td>
<td>267 (53.4)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>17 (13.7)</td>
<td>18 (14.3)</td>
<td>20 (15.9)</td>
<td>18 (14.5)</td>
<td>.99</td>
<td>73 (14.6)</td>
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<tr>
<td>Sulfonylurea</td>
<td>40 (32.3)</td>
<td>41 (32.5)</td>
<td>41 (32.5)</td>
<td>38 (30.6)</td>
<td>.99</td>
<td>160 (32.0)</td>
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<tr>
<td>Time since diabetes diagnosis, median (IQR), y</td>
<td>1.6 (0.2-5.0)</td>
<td>2.7 (0.4-5.7)</td>
<td>1.2 (0.2-6.2)</td>
<td>2.0 (0.3-6.3)</td>
<td>.25</td>
<td>2.0 (0.2-5.6)</td>
</tr>
<tr>
<td>HbA1c, median (IQR), %</td>
<td>6.9 (6.4-8.0)</td>
<td>6.9 (6.3-7.5)</td>
<td>6.7 (6.3-7.4)</td>
<td>7.1 (6.4-7.9)</td>
<td>.03</td>
<td>6.9 (6.3-7.7)</td>
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<tr>
<td>Geometric mean (95% CI)</td>
<td>7.2 (7.0-7.3)</td>
<td>7.0 (6.9-7.2)</td>
<td>6.8 (6.7-7.3)</td>
<td>7.1 (7.0-7.4)</td>
<td>.04</td>
<td>7.0 (7.0-7.1)</td>
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<tr>
<td>Fasting SMBG, median (IQR), mg/dL</td>
<td>169 (143-194)</td>
<td>161 (138-191)</td>
<td>165 (143-188)</td>
<td>168 (147-194)</td>
<td>.59</td>
<td>165 (143-192)</td>
</tr>
<tr>
<td>Geometric mean (95% CI)</td>
<td>168 (161-175)</td>
<td>160 (154-167)</td>
<td>163 (156-170)</td>
<td>165 (158-172)</td>
<td>.44</td>
<td>164 (161-168)</td>
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<tr>
<td>2-h postprandial SMBG, median (IQR), mg/dL</td>
<td>194 (163-234)</td>
<td>191 (166-217)</td>
<td>195 (166-217)</td>
<td>196 (164-238)</td>
<td>.67</td>
<td>195 (165-227)</td>
</tr>
<tr>
<td>Geometric mean (95% CI)</td>
<td>194 (186-203)</td>
<td>191 (182-199)</td>
<td>191 (183-200)</td>
<td>196 (188-205)</td>
<td>.76</td>
<td>193 (189-197)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CI, confidence interval; HbA1c, 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.

aP values for any difference in groups derived from the χ² test for categorical variables, analysis of variance for means, or Kruskal-Wallis for median values.

bBody mass index (BMI) calculated as weight in kilograms divided by height in meters squared.
term 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 run-in and were screened for eligibility (FIGURE 1). Baseline characteristics of participants are provided in TABLE 1.

Change in Glucose and HbA1c

Levels and Weight

Glucose and HbA1c 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). HbA1c 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 condition on baseline hsCRP level, and expanded multivariable models additionally adjusted for baseline HbA1c 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 HbA1c 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 anti-diabetic therapy or statin medications (n = 33) were excluded from the analysis. Effects of the study treatments on IL-6 and sTNFα 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

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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 glargine 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-

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

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

**Abbreviations:** CI, confidence interval; hsCRP, high-sensitivity C-reactive protein.

bAdjusted for baseline treatment stratum, conditioned on baseline hsCRP.

bP value for comparison with no intervention or placebo as appropriate.

bAdditionally adjusted for baseline glycated hemoglobin level, weight, and change in weight at each time point.

bP value for the prespecified comparison of those allocated to metformin and insulin with metformin alone = .55.

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substantially 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 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.

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), 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, although data in this regard are sparse. Because visceral fat is closely linked with subclinical inflammation, 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 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 HbA1c levels. However, adjustment for baseline differences in biomarker levels and weight change were not uniformly performed. In 1 recent study 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, 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 studies demonstrate hsCRP lowering with a broad range of short-
In conclusion, despite substantially improving glucose control, neither insulin nor metformin improved inflammatory status among individuals with type 2 diabetes initiating therapy. From a physiologic perspective, these data provide insights into the complex interrelationships that underlie inflammation and atherosclerosis in diabetic patients. From a clinical perspective, until other end-point trial data become available, 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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