Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus

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Background: We investigated whether metformin hydrochloride has sustained beneficial metabolic and (cardio)vascular effects in patients with type 2 diabetes mellitus (DM2).

Methods: We studied 390 patients treated with insulin in the outpatient clinics of 3 hospitals in a randomized, placebo-controlled trial with a follow-up period of 4.3 years. Either metformin hydrochloride, 850 mg, or placebo (1-3 times daily) was added to insulin therapy. The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality, as separate aggregate scores. In addition, effects on hemoglobin A1c (HbA1c), insulin requirement, lipid levels, blood pressure, body weight, and body mass index were analyzed.

Results: Metformin treatment prevented weight gain (mean weight gain, −3.07 kg [range, −3.85 to −2.28 kg]; P < .001), improved glycemic control (mean reduction in HbA1c level, 0.4% percentage point [95% CI, 0.55-0.25]; P < .001) (where CI indicates confidence interval), despite the aim of similar glycemic control in both groups, and reduced insulin requirements (mean reduction, 19.63 IU/d [95% CI, 24.91-14.36 IU/d]; P < .001). Metformin was not associated with an improvement in the primary end point. It was, however, associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61 [95% CI, 0.40-0.94; P = .02), which was partly explained by the difference in weight. The number needed to treat to prevent 1 macrovascular end point was 16.1 (95% CI, 9.2-66.6).

Conclusions: Metformin, added to insulin in patients with DM2, improved body weight, glycemic control, and insulin requirements but did not improve the primary end point. Metformin did, however, reduce the risk of macrovascular disease after a follow-up period of 4.3 years. These sustained beneficial effects support the policy to continue metformin treatment after the introduction of insulin in any patient with DM2, unless contraindicated.

Trial Registration: ClinicalTrials.gov Identifier: NCT00375388

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The rising incidence of type 2 diabetes mellitus (DM2) makes it an increasingly important cause of cardiovascular disease (CVD) and death. Up to 75% of patients with DM2 will die from a cardiovascular complication. Therefore, prevention of cardiovascular complications in patients with DM2 is crucial.

Questions remain concerning the beneficial effects of metformin hydrochloride in patients with DM2. To our knowledge, the only randomized intervention trial on this subject was the UK Prospective Diabetes Study (UKPDS), the results of which suggest a cardioprotective role for metformin. However, the design and analyses of the UKPDS have raised considerable debate. Nevertheless, data from cohort studies support the results from the UKPDS but the need for clinical, randomized intervention trials still exists to help clarify this issue. In addition, the mechanisms through which metformin may decrease the risk of microvascular and macrovascular disease are unclear and may include reduction of weight gain and hyperinsulinemia, improvement of endothelial function and fibrinolysis, and reduction of low-grade inflammation, oxidative stress, and glycation.

Type 2 diabetes mellitus is a progressive disease, and many patients will need treatment with insulin during the course
of the disease. Several short-term studies in insulin-treated patients with DM2 have shown that metformin can improve glycemic control and reduce insulin requirements and weight gain. To our knowledge, the long-term beneficial effects of metformin in such patients have not been studied.

We hypothesized that, in patients with DM2 treated with insulin, metformin, compared with placebo, will have sustained beneficial metabolic effects, even at the same level of glycemic control, and thus decrease (cardio)vascular disease. We designed the randomized, placebo-controlled, multicenter trial “Hyperinsulinemia: the Outcome of Its Metabolic Effects (HOME)” to investigate these issues during a planned follow-up period of 4.3 years.

METHODS

PATIENTS

We included 390 patients with DM2 (age range, 30-80 years) as previously described. All patients gave written informed consent. The medical ethical committees of the 3 participating hospitals approved the trial protocol. The trial was conducted in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) dated July 17, 1996, and in accordance with the Declaration of Helsinki (revised versions of Hong Kong in 1989 and Edinburgh, Scotland, in 2000).

STUDY DESIGN

The HOME Trial was conducted in the outpatient clinics of 3 hospitals (in the cities of Hoogeveen, Meppel, and Coevorden, the Netherlands). Patients were randomly allocated to either placebo or metformin by aid of a computer program, which allocated a random number to identical-looking boxes of either metformin or placebo. The trial design consisted of 3 phases, as shown in Figure 1.

GLYCEMIC CONTROL AND INSULIN TITRATION

In the prerandomization phase, we aimed to optimize glycemic control by intensive glucose monitoring and insulin adjustments (target glucose levels, fasting: 72.1-126.1 mg/dL, and postprandial: 72.1-180.2 mg/dL). (To convert glucose to millimoles per liter, multiply by 0.0555.) All subjects monitored their glucose levels at home every 2 weeks (ie, just before and roughly 90 minutes after breakfast, lunch, and dinner, and at bedtime) using the same monitoring device (Glucotouch; Lifescan, Beerse, Belgium). Individual insulin titration took place according to good clinical practice to reach the target glucose levels and to prevent hypoglycemia. If the target values for glycemic control were difficult to reach, the study nurse consulted the principal investigator for advice on how to optimize the insulin therapy. This glucose-monitoring and insulin adjustment scheme was continued during the whole trial, as detailed elsewhere.

CLINICAL END POINTS

The study was designed to examine the effects of metformin on metabolic and disease-related end points, as previously described (Table 1). The metabolic end points examined were body weight, body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, waist-to-hip ratio (WHR), hemoglobin A1c (HbA1c), home-monitored concentraions of preprandial and postprandial glucose, fasting plasma insulin, and the daily dose of insulin. We also collected data on blood pressure (BP) and plasma lipids. In addition, we collected information on the incidence of hypoglycemic events. A hypoglycemic event was defined as a blood glucose concentration below 68.5 mg/dL with symptoms of hypoglycemia or a value below 54.1 mg/dL, with or without such symptoms. Data on weight, HbA1c, home-monitored concentrations of preprandial and postprandial glucose levels, and BP were obtained at each visit (every 3 months). Waist-to-hip ratio was measured at baseline and after 4, 7, and 48 months. Plasma lipid levels were measured at baseline and every 6 months thereafter; plasma insulin level was measured at baseline, after 4 months, and every 12 months thereafter.

On the assumption that several shared determinants of macrovascular and microvascular disease (eg, hypertension, obesity, endothelial dysfunction, and chronic inflammation) might be influenced by metformin, the primary end point was constructed as a combination of macrovascular and microvascular disease. Secondary disease-related end points were macrovascular and microvascular disease separately (Table 1). Before disclosure of the treatment codes, an independent scientific committee (1 specialist in vascular medicine and 1 specialist in endocrinology) checked the registration, or absence thereof, of all disease-related end points. No misreporting was found.

To optimally study the metabolic end points, patients continued to participate in the trial after the occurrence of a nonfatal disease–related end point, unless a contraindication for...
metformin emerged. Therefore, a patient who completed the planned 4.3-year follow-up period (a “completer”) may or may not have encountered a disease-related end point. A noncompleter could thus have been withdrawn before the final visit for a variety of reasons: adverse effects, withdrawal of consent, loss to follow-up, a fatal end point, or because of the development of a contraindication to metformin, notably renal or heart failure (New York Heart Association class III/IV). We screened for renal failure by monitoring creatinine clearance. Patients with a creatinine clearance in the range of 40 to 60 mL/min/1.73 m² were allowed a maximum of two 850-mg tablets per day; those with a range of 30 to 40 mL/min/1.73 m² were allowed one 850-mg tablet per day; and those below 30 mL/min/1.73 m² were withdrawn from the study. (To convert creatinine clearance to milliliters per second per meters squared, multiply by 0.0167.)

STATISTICAL ANALYSES

Sample Size and Power Analysis

The planned study sample size of 390 patients was based on an expected difference in the occurrence of the primary end point of at least 8% points between the treatment groups after 4.3 years, with an expected incidence of 20% in the placebo group and 12% in the metformin group (1-tailed t test on proportional hazard regression with α=0.05 and β=0.25).

Data Analysis

The data presented herein concern all randomized patients (intention-to-treat [ITT] sample; n=390); 95% confidence intervals (CIs) are used, and P values for the individual variables represent 2-sided t tests.

The effects of metformin on the metabolic end points were assessed by analyzing the complete time course for each variable. For this purpose, the summary mean (mean score of non-missing values over the entire observation period) constitutes the appropriate repeated measurement technique.16 This summary mean was then compared between the treatment groups through an analysis of covariance, while adjusting for baseline values and baseline differences in age, sex, smoking, and the prior occurrence and severity of CVD. The χ² test was used to compare the number of hypoglycemic events between the 2 treatment groups. The effects of metformin on the disease-related end points were assessed by comparing time to first event by means of proportional hazards multiple regression analyses. This was the primary analysis for both the primary and the secondary end points. Because of the baseline differences in age, sex, smoking, and the prior occurrence and severity of CVD between the 2 treatment groups, we adjusted for these variables in all analyses. As an additional analysis, a multiple end point survival technique was used to take into account multiple events.17

### Table 1. Metabolic and Disease-Related End Points of the HOME Trial

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Myocardial infarction</td>
<td>Documented diagnosis by a cardiologist</td>
</tr>
<tr>
<td>2. Heart failure</td>
<td>Documented diagnosis by a cardiologist</td>
</tr>
<tr>
<td>3. Changes of ECG</td>
<td>Minnesota scores 1.1-1.3, 4.1-4.3, 5.1-5.3, 7.1</td>
</tr>
<tr>
<td>4. Acute coronary syndrome</td>
<td>Documented diagnosis by a cardiologist; having resulted in hospital admission</td>
</tr>
<tr>
<td>5. Diabetic foot</td>
<td>Documented diagnosis by a neurologist</td>
</tr>
<tr>
<td>6. Stroke</td>
<td>Documented diagnosis by a cardiologist</td>
</tr>
<tr>
<td>7. Transient ischemic attack</td>
<td>Documented diagnosis by a neurologist</td>
</tr>
<tr>
<td>8. Peripheral arterial disease</td>
<td>Diagnosed by angiography</td>
</tr>
<tr>
<td>9. Peripheral arterial reconstr</td>
<td>Determined by a physician and well documented in the original medical record and in the CRF</td>
</tr>
<tr>
<td>10. PTCA</td>
<td>Determined by a physician and well documented in the original medical record and in the CRF</td>
</tr>
<tr>
<td>11. CABG</td>
<td>Determined by a physician and well documented in the original medical record and in the CRF</td>
</tr>
<tr>
<td>12. Nontraumatic amputation</td>
<td>Determined by a physician and well documented in the original medical record and in the CRF</td>
</tr>
<tr>
<td>13. Sudden death</td>
<td>Determined by a physician and well documented in the original medical record and in the CRF</td>
</tr>
<tr>
<td>14. Progression of retinopathy</td>
<td>Classified by an ophthalmologist (A → C or B → C), where A indicates none; B, nonproliferative; C, proliferative</td>
</tr>
<tr>
<td>15. Progression of nephropathy</td>
<td>A → B or A → C or B → C; expressed as albuminuria (albumin to creatinine ratio in urine, A/C in milligrams per millimole), where A indicates normoalbuminuria; B, microalbuminuria; C, macroalbuminuria. Men were normal at A/C &lt; 2.5; had microalbuminuria at 2.5 - A/C &lt; 25, and had macroalbuminuria at &gt;25. Women were normal at A/C &lt; 3.5, had microalbuminuria at 3.5 - A/C &lt; 35, and had macroalbuminuria at &gt;35.</td>
</tr>
<tr>
<td>16. Progression of neuropathy (A → B or A → C or A → D or B → C or B → D or C → D, with a difference in score of at least 6 points)</td>
<td>Diabetic polyneuropathy was evaluated by constructing a neuropathy score, where A indicates normal or 0 points; B, mild, 1-9 points; C, moderate, 10-18 points; D, severe, 19-33 points.</td>
</tr>
<tr>
<td>17. Death by other cause</td>
<td>Noncardiovascular nonsudden death</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass graft; CRF, clinical research file; ECG, electrocardiogram; HOME, Hyperinsulinemia: the Outcome of its Metabolic Effects; PTCA, percutaneous transluminal coronary angioplasty.

1a The metabolic end points were lipid profile, body weight, body mass index, waist-to-hip ratio, plasma hemoglobin A1c concentration, home-monitored concentrations of preprandial and postprandial glucose, plasma insulin concentration, daily dose of insulin, blood pressure, plasma lipids. The primary end points were clinical events 1 to 16, and secondary end points were as follows: (1) macrovascular: clinical events 1 to 13 and (2) microvascular: clinical events 14 to 16.

b See Valk et al.12
by the metformin-associated changes in the metabolic end points, we used proportional hazards multiple regression analysis to reanalyze the HRs after adjusting for metabolic variables. Main effects and first-order interaction with treatments were tested, and nonsignificant effects (P < .05) were sequentially removed to reduce type I errors and promote stability of the model.

**RESULTS**

**PATIENTS**

We screened the medical files of all 3 participating outpatient clinics and identified 745 eligible patients. All were approached to enroll into the trial, and 390 subjects gave written informed consent. A total of 196 subjects were randomized to receive metformin and 194 to receive placebo. Of the 390 included patients, 277 subjects (72%) completed the HOME Trial (completers). Of the noncompleters, 46 experienced adverse events (30 metformin, 16 placebo), 3 patients developed a contraindication to metformin (1 liver failure [metformin]; 2, heart failures [1 metformin, 1 placebo]), 15 encountered a fatal disease–related end point (9 metformin, 6 placebo), 47 withdrew their consent (22 metformin, 25 placebo), and 2 patients were lost to follow-up (2 metformin). Of the 46 patients with adverse events, 33 experienced diarrhea (22 metformin, 11 placebo); 20, flatulence (10 metformin, 10 placebo); 15, fatigue (7 metformin, 8 placebo); 14, pruritus (5 metformin, 9 placebo); 15, headaches (6 metformin, 9 placebo); 16, heartburn (7 metformin, 9 placebo); and 20, nausea (10 metformin, 10 placebo). Noncompleters did not differ from completers with respect to duration of DM2, prior occurrence and severity of CVD, age, or weight. More women than men were noncompleters (male to female ratio, 1:1.8 metformin vs 1:1 placebo; P = .01).

**Table 2** shows baseline characteristics of all randomized patients. Patients randomized to metformin were slightly older than patients randomized to placebo (mean [SD] age, 63.6 [9.6] vs 59.1 [11.0] years, respectively), had a more extensive cardiovascular history (1.17 vs 0.92, respectively) and were less often smokers. The other characteristics were comparable between the treatment groups. The actual mean daily doses in the metformin group in the short- and long-term treatment phases were 2163 mg and 2050 mg, respectively. Although the use of statins was low at baseline, in accordance with treatment guidelines at the start of the study, its use increased to 67 patients in the metformin group and 54 patients in the placebo group at the final visit.

**METABOLIC END POINTS**

**Improved Glycemic Control and Reduced Insulin Requirements With Metformin**

Despite the aim of similar glycemic control in both groups, after 4.3 years of treatment, the mean difference in the summary mean for HbA1c, between the metformin and placebo groups was −0.40 percentage point (−0.55 to −0.25; P < .001) (to convert HbA1c to a proportion of total hemoglobin, multiply by 0.01). For home-monitored concentrations of preprandial and postprandial glucose, the mean differences were −5.2 mg/dL (range, −9.2 to −1.3 mg/dL; P = .01) and −7.9 mg/dL (range, −12.3 to −3.6 mg/dL; P < .01), respectively. For plasma insulin, the mean difference was −17.85 µIU/mL (range, −33.26 to −2.30 µIU/mL; P = .02) (to convert serum insulin to picomoles per liter, multiply by 6.945). For the daily dose of insulin, the mean difference was −19.63 IU/d (range, −24.91 to −14.36 IU/d; P < .001) or −0.18 IU/kg (range, −0.23 to −0.12 IU/kg; P < .001) (**Table 3** and [Figure 2 and Figure 3]).

**Use of Metformin to Prevent Weight Gain**

After 4.3 years of treatment, the mean difference in the summary mean for body weight between the metformin and placebo groups was −3.07 kg (range, −3.85 to −2.28 kg; P < .001). The mean difference for BMI was −1.09 (95% CI, −1.37 to −0.81; P < .001). The mean difference for the WHR was −0.015 (95% CI, −0.029 to −0.001; P = .04) (**Figure 3**).
No Decrease in BP With Metformin

After 4.3 years of treatment, the mean difference in the summary mean between the metformin and placebo groups was −0.51 mm Hg (range, −2.76 to 1.44 mm Hg; P = .38) for systolic BP and −0.88 mm Hg (−3.21 to 1.45 mm Hg; P = .46) for diastolic BP.

No Improvement in Plasma Lipid Profile With Metformin

After 4.3 years of treatment, the difference in the summary mean between the metformin and placebo groups was −0.77 mg/dL (range, −4.63 to 6.18 mg/dL; P = .78) for total cholesterol level; 0.00 mg/dL (−4.63 to 4.63 mg/dL; P = .98) for low-density lipoprotein cholesterol level; 0.88 mg/dL (−0.73 to 12.39; P = .82) for triglyceride level; and 0.00 mg/dL (−123.9 to 56.0 mg/dL; P = .91) for high-density lipoprotein cholesterol level. The use of lipid-lowering drugs did not significantly differ between the groups (P = .45), and adjustment for use of lipid-lowering drugs did not change the results. (To convert total, low-density high-density cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.)

HYPOGLYCEMIC EVENTS

After 4.3 years of treatment, no difference in the number of hypoglycemic events between the metformin and placebo groups existed (metformin, 2.1 events vs placebo, 2.6 total hypoglycemic events per person per year; P = .89). In 0.3 and 0.3 events per person per year, respectively, help from others was needed (P = .33).

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors. To convert serum glucose to millimoles per liter, multiply by 0.0555; to convert plasma HbA1C to a proportion of total hemoglobin, multiply by 0.01; to convert serum insulin to picomoles per liter, multiply by 6.945; to convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

Table 3. Overview of the Main End Points: Metabolic End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo Group (n=194)</th>
<th>Summary Mean</th>
<th>Placebo Group (n=194)</th>
<th>Summary Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>87 (15)</td>
<td>91 (17)</td>
<td>90 (16)</td>
<td>85 (16)</td>
</tr>
<tr>
<td>BMI</td>
<td>30 (5)</td>
<td>31 (5)</td>
<td>31 (5)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>Men 1.03 (0.1)</td>
<td>1.03 (0.1)</td>
<td>1.03 (0.1)</td>
<td>1.02 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Women 0.93 (0.1)</td>
<td>0.95 (0.1)</td>
<td>0.94 (0.1)</td>
<td>0.92 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Plasma HbA1C level, %</td>
<td>7.9 (1.2)</td>
<td>7.9 (1.1)</td>
<td>7.9 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Preprandial glucose level, mg/dL</td>
<td>158.6 (32.4)</td>
<td>144.1 (27.0)</td>
<td>147.7 (28.8)</td>
</tr>
<tr>
<td></td>
<td>Postprandial glucose level, mg/dL</td>
<td>183.8 (36.0)</td>
<td>162.2 (28.8)</td>
<td>169.4 (23.4)</td>
</tr>
<tr>
<td></td>
<td>Serum insulin level, µIU/mL</td>
<td>43.3 (98.8)</td>
<td>75.2 (153.8)</td>
<td>79.0 (138.4)</td>
</tr>
<tr>
<td></td>
<td>Daily dose of insulin, IU/d</td>
<td>64 (25)</td>
<td>100 (59)</td>
<td>64 (40)</td>
</tr>
<tr>
<td></td>
<td>Systolic BP, mm Hg</td>
<td>159 (25)</td>
<td>141 (14)</td>
<td>154 (17)</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP, mm Hg</td>
<td>86 (11)</td>
<td>79 (10)</td>
<td>85 (9)</td>
</tr>
<tr>
<td></td>
<td>Plasma total cholesterol level, mg/dL</td>
<td>212.4 (50.2)</td>
<td>162.2 (30.9)</td>
<td>181.5 (34.7)</td>
</tr>
<tr>
<td></td>
<td>Plasma LDL cholesterol level, mg/dL</td>
<td>131.3 (38.6)</td>
<td>84.9 (23.2)</td>
<td>104.2 (30.9)</td>
</tr>
<tr>
<td></td>
<td>Plasma triglyceride level, mg/dL</td>
<td>168.1 (132.7)</td>
<td>141.6 (141.6)</td>
<td>150.4 (106.2)</td>
</tr>
<tr>
<td></td>
<td>Plasma HDL cholesterol level, mg/dL</td>
<td>48.3 (15.4)</td>
<td>51.4 (15.4)</td>
<td>49.0 (15.4)</td>
</tr>
</tbody>
</table>

Bibliographic references have been omitted. For the complete reference list, see the Table 4 and Figure 4.

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neuropathy, the HR for the secondary, microvascular end point was 1.04 (95% CI, 0.75-1.44; *P* = .43).

**ADDITIONAL ANALYSES**

After adjusting for the change in weight, the HR for the secondary, macrovascular end point was 0.77 (95% CI, 0.55-1.09; *P* = .33) compared with 0.60 (95% CI, 0.40-0.92; *P* = .04) without adjusting for change in weight. However, adjustments for the metformin-associated changes in other metabolic efficacy variables, such as BP or lipid profile, did not materially change our results. For example, after adjusting for changes in HbA1c level, daily dose of insulin, and systolic BP, the HR for the secondary, macrovascular end point was 0.34 (95% CI, 0.21-0.56; *P* = .001) compared with 0.60 (95% CI, 0.40-0.92; *P* = .04) without such adjustments. The HR for the secondary macrovascular end point without including diabetic foot was 0.60 (95% CI, 0.44-0.85; *P* = .05) compared with 0.60 (95% CI, 0.40-0.92; *P* = .04). There was no interaction between hospital center and treatment, and adjustment for treatment center did not change any of the results. Analyses using the per protocol population showed similar results, although slightly more in favor of metformin, compared with the ITT population. Analysis of the metabolic end points using the last observation carried forward instead of the summary mean yielded very similar results.

There was loss of glycemic control over time (Figure 2), which was similar in both groups. In the placebo and metformin groups, 14% and 16% of patients, respectively, had an HbA1c level of less than 7% at the final visit, and in both groups 14% of patients had an HbA1c level higher than 8% at the final visit while having had an HbA1c lower than 7% at baseline. Conversely, 10% and 9% of patients in the placebo and metformin groups, respectively, had an HbA1c level lower than 7% at the final visit, while having had an HbA1c level higher than 8% at baseline.

**COMMENT**

Our study on the effects of long-term metformin treatment in patients with DM2 treated with insulin had 2 main findings. First, metformin treatment was associated with beneficial effects on outcomes such as body weight and insulin requirements and with moderately beneficial effects on glycemic control (despite the aim of similar glycemc control in both groups), but not on BP and the plasma lipid profile. Second, metformin treatment did not decrease the risk of the primary end point but did decrease the risk of the secondary, macrovascular end point.

The favorable effects of metformin treatment on weight gain and insulin requirements are in accordance with previous findings from short-term studies. The absence of a BP-lowering effect of metformin is also consistent with previous studies and meta-analyses. Previous short-term studies on plasma lipid levels have shown either no benefit or only a small effect of metformin treatment. Importantly, our study shows that the beneficial effects on weight gain and insulin requirements persisted during 4.3 years of follow-up. The reductions of the daily dose of insulin and of plasma insulin levels seem to indicate lower insulin exposure levels in the metformin group.

The beneficial effects of metformin on weight and on insulin requirements continued to improve during 4.3 years of treatment. The improvements in glycemic control, however, occurred rapidly but were not maintained throughout the long treatment period. The rate of the loss of glycemic control (approximately 1 percentage point increase in HbA1c level over 5 years) was similar to that seen in the UKPDS. It is unclear why this loss of glycemic control, which was comparable between the
treatment groups, occurred. Insulin adjustments were made based on a treatment protocol, using target glucose values. Glycemic control deterioration after initial improvement has been frequently described before; a higher risk of glycemic relapse has been associated with insulin treatment, longer duration of DM2, and weight.

Table 4. Overview of the Main End Points: Disease-Related End Pointsa

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo Group (n=194)</th>
<th>Metformin Hydrochloride Group (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Last Visit</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21 (11)</td>
<td>25 (13)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Ischemic changes of ECG</td>
<td>NA</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Diabetic foot</td>
<td>6 (3)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>10 (5)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>10 (5)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Cardiovascular intervention</td>
<td>18 (9)</td>
<td>27 (14)</td>
</tr>
<tr>
<td>Nontraumatic amputation</td>
<td>3 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>NA</td>
<td>1 (1)b</td>
</tr>
<tr>
<td>Progression of retinopathy</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Progression of nephropathy</td>
<td>NA</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Progression of neuropathy</td>
<td>NA</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Death by other causes</td>
<td>NA</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; NA, not applicable.

a Data are given as number (percentage). Differences (with P values) between metformin and placebo (Figures 3 and 4) are described in more detail in the “Disease-Related End Points” subsection in the “Results” section.

b Cardiovascular death.

c Three cardiovascular deaths and 1 fatal car crash.

Figure 3. Insulin requirements and weight. The summary means were significantly different between the groups for A, daily dose of insulin (P<.001); B, body weight (P<.001); C, fasting plasma insulin (P=.02); and D, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) (P<.001). To convert serum insulin from picomoles per liter to micro–international units per milliliter, divide by 6.945.
gain. In addition, glycemic relapse has been, at least partly, attributed to the progressive nature of DM2. Indeed, in our study, higher insulin dosages were needed over time, especially in the placebo group. A reluctance of both physician and patient to increase the insulin dosage in the face of deteriorating glycemic control has been described as a strong contributor to the deterioration of glycemic control. Our study nurses, however, carefully performed the protocol for glycemic control during the whole period of follow-up.

Overall, glycemic control was better in the metformin group, despite the aim of similar glycemic control in both groups. These data suggest that, in patients with DM2 treated with insulin, metformin may affect glucose metabolism by improving the hepatic responsiveness to insulin and by increasing the release of glucagon-like peptide type 1.

To our knowledge, no randomized, placebo-controlled trials on the effects of metformin on macrovascular or microvascular disease in patients with insulin-treated DM2 have been reported. In our study, metformin treatment was associated only with favorable effects on macrovascular disease but, somewhat unexpectedly, not on microvascular disease. Several reasons may account for this. In studies that have shown improved microvascular outcomes in treated patients with DM2, larger HbA1c differences were maintained over longer periods of time. In addition, improvements in BP have been shown to be an important contributor to a decrease in microvascular disease risk. Thus, the small effect of metformin on glycemic control and the lack of an effect on BP may explain why microvascular outcomes were not improved within the follow-up period of 4.3 years. The absence of a treatment effect on microvascular disease may explain why significant changes were not observed in the primary end point (P = .33), in which microvascular events were incorporated.

In our study, the favorable effects of metformin on macrovascular disease could be partly explained (roughly 40%) by the metformin-associated change in weight. All other metformin-associated changes in metabolic or hemodynamic variables, such as HbA1c level and daily dose of insulin, did not seem to contribute to the favorable effect of metformin on macrovascular disease. Taken together, these results suggest that metformin affects CVD partly by reducing weight, but that mechanisms other than improving glycemic control or reducing insulin requirements may be of importance as well. Previous studies have shown metformin to improve endothelial function and fibrinolysis, independent of glycemic control, insulin requirements, or weight gain. Endothelial dysfunction, in turn, has been strongly associated with an increased risk of CVD. Metformin-associated improvements in endothelial function, however, were small. Other possible mechanisms may include effects on advanced glycation end product levels or the secretion of adipocyte-derived mediators (eg, free fatty acids, leptin, resistin, and adiponectin). These possible mechanisms require further investigation.

Strengths of our study include its randomized, placebo-controlled, double-blind design, its long follow-up period of 4.3 years, and finally the sustained participation of patients in the trial after the occurrence of a nonfatal disease–related end point, thereby reducing dropout bias. In addition, the results were consistent across the different statistical analyses used.

Our study has several limitations. First, its relatively small sample size and consequently limited power may have obscured smaller treatment effects. To increase the power of our study, disease-related end points were constructed by combining separate clinical events regarding microvascular and macrovascular disease. An assumption in the construction of these disease-related end points is that its components are equally important, which is not necessarily true. In addition, the hypothesis that metformin influences both microvascular and macrovascular disease through shared underlying pathophysiologic characteristics, in the way, for instance, that obesity does, may not be correct. Diabetic foot was included in the primary end point, a combination of microvascular and macrovascular disease, as well as in the secondary, macrovascular end point. The etiology of diabetic foot lesions is a complex issue, but it is recognized that 3 key elements are involved: neuropathy, peripheral vascular disease, and infection. Five of the 8 patients who developed a diabetic foot showed marked peripheral vascular disease on angiographic examination during their hospital admission. However, 3 patients had no angiographic documentation and could have developed a diabetic foot without any peripheral arterial disease. However, the HR for the secondary macrovascular end point without including diabetic foot was 0.60 (95% CI, 0.44-0.85; P = .05) compared with 0.60 (95% CI, 0.40-0.92; P = .04). Second, there was an imbalance between the 2 treatment groups after randomization. We adjusted for this in all analyses. To adjust for the difference in prior CVD, we constructed a way of measuring cardiovascular...
Data analysis.

In conclusion, we showed that in patients with DM2 treated with insulin, the addition of metformin resulted in improvements in weight, glycemic control, and insulin requirements, which were maintained after 4.3 years of treatment. However, metformin treatment did not reduce the risk of the primary end point. It may, however, reduce the risk of macrovascular disease, independently of reducing hyperinsulinemia, but partly related to the prevention of weight gain during insulin treatment. In general practice, when, owing to the progressive nature of DM2, insulin treatment is required, patients may benefit if metformin treatment is continued.

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