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Metformin versus placebo in combination with insulin analogues in patients with type 2 diabetes mellitus—the randomised, blinded Copenhagen Insulin and Metformin Therapy (CIMT) trial

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ABSTRACT

Objective: To assess the effect of metformin versus placebo both in combination with insulin analogue treatment on changes in carotid intima-media thickness (IMT) in patients with type 2 diabetes.

Design and setting: Investigator-initiated, randomised, placebo-controlled trial with a 2×3 factorial design conducted at eight hospitals in Denmark.

Participants and interventions: 412 participants with type 2 diabetes (glycated haemoglobin (HbA_{1c}) ≥7.5% (≥58 mmol/mol); body mass index >25 kg/m2) were in addition to open-labelled insulin treatment randomly assigned 1:1 to 18 months blinded metformin (1 g twice daily) versus placebo, aiming at an HbA_{1c} ≤7.0% (≤53 mmol/mol).

Outcomes: The primary outcome was change in the mean carotid IMT (a marker of subclinical cardiovascular disease). HbA_{1c}, insulin dose, weight and hypoglycaemic and serious adverse events were other prespecified outcomes.

Results: Change in the mean carotid IMT did not differ significantly between the groups (between-group difference 0.012 mm (95% CI −0.003 to 0.026), p=0.11). HbA_{1c} was more reduced in the metformin group (between-group difference −0.42% (95% CI −0.62% to −0.23%), p<0.001)), despite the significantly lower insulin dose at end of trial in the metformin group (1.04 IU/kg (95% CI 0.94 to 1.15)) compared with placebo (1.36 IU/kg (95% CI 1.23 to 1.51), p<0.001). The metformin group gained less weight (between-group difference −2.6 kg (95% CI −3.3 to −1.8), p<0.001). The groups did not differ with regard to number of patients with severe or non-severe hypoglycaemic or other serious adverse events, but the metformin group had more non-severe hypoglycaemic episodes (4347 vs 3161, p<0.001).

Conclusions: Metformin in combination with insulin did not reduce carotid IMT despite larger reduction in HbA_{1c}, less weight gain, and smaller insulin dose compared with placebo plus insulin. However, the trial only reached 46% of the planned sample size and lack of power may therefore have affected our results.

Trial registration number: NCT00657943; Results.

Strengths and limitations of this study

- Recent meta-analyses have questioned the evidence for cardiovascular benefits of metformin whether used alone or in combination with other glucose lowering drugs in patients with type 2 diabetes. The Copenhagen Insulin and Metformin Therapy (CIMT) trial was designed to address this question.
- Strengths of the CIMT trial include the centrally randomised, placebo-controlled blinded design and the relatively large population of well-characterised patients.
- A limitation is the choice of carotid intima-media thickness as a surrogate risk marker for cardiovascular disease instead of using clinical hard outcomes.
- The trial only reached 46% of the planned sample size and lack of power may therefore have affected our results.

INTRODUCTION

Individuals with type 2 diabetes have increased risk of cardiovascular morbidity and mortality.[1] Observational studies have shown a positive association between level of glycated haemoglobin (HbA_{1c}) and development of cardiovascular disease.[2 3] Whether a reduction in HbA_{1c} leads to a reduction in risk of cardiovascular disease remains controversial.[4 5] Metformin is recommended as the preferred first-line glucose lowering drug in patients not reaching their individual glycaemic targets on lifestyle treatment.[6] Most patients will need other glucose lowering drugs including insulin to control hyperglycaemia. Patients treated with insulin may in principle not need other glucose lowering drugs to reach glycaemic targets, but several clinical guidelines recommend metformin as an adjunct to insulin primarily due to less weight gain, reduced HbA_{1c} and less insulin requirement compared with insulin treatment alone.[7 8] An additional argument is the putative cardiovascular benefits of metformin.[8 9] However, recent meta-analyses have questioned the evidence for cardiovascular benefits of metformin whether used alone or in combination with other glucose lowering drugs in patients with type 2 diabetes.[10–12]

Carotid intima-media thickness (IMT) comprises the combined thickness of the tunica intima and media in the carotid artery wall. It is measured non-invasively by ultrasound with good reproducibility.[13] Carotid IMT is frequently used in clinical research as a risk marker for cardiovascular disease and has been shown to correlate with established and future cardiovascular disease.[14 15]

The primary objective of the Copenhagen Insulin and Metformin Therapy (CIMT) trial was to assess the effect of 18 months intervention with metformin versus placebo in combination with three insulin analogue regimens on changes in carotid IMT in patients with type 2 diabetes. We hypothesised that intervention with metformin in combination with insulin could reduce the progression of carotid IMT compared with placebo in combination with insulin.

The effects of the three insulin regimen comparisons are reported in a separate manuscript.[16]

MATERIALS AND METHODS

Trial design, participants and randomisation

The CIMT trial is an investigator initiated, multicentre, randomised, placebo controlled superiority trial with a 2×3 factorial design conducted from May 2008 to December 2012 at eight hospitals in the capital region of Denmark.[17] Inclusion criteria were: patients with type 2 diabetes, age >30 years, body mass index >25 kg/m^2, HbA_{1c} ≥7.5% (58 mmol/mol), treatment with oral antidiabetic drugs for ≥1 year, and/or insulin treatment for ≥3 months. Exclusion criteria were major cardiovascular disease within the past 3 months, carotid artery stenosis >70%, heart failure, recent cancer, renal or liver disease, alcohol or drug abuse, unstable retinopathy, pregnant or breastfeeding women, fertile women not using anticonception or allergy towards trial medication. All participants provided written informed consent before participation.

Central randomisation at the Copenhagen Trial Unit was conducted according to a computer generated allocation sequence in two steps according to the 2×3 factorial design. Randomisation was in the first step performed using permuted blocks with varying block sizes of four, six and eight and in the second step using varying block sizes of three, six and nine. Participants were in the first step randomised 1:1 to 18 months blinded treatment with metformin versus placebo. In the second step, participants were randomised 1:1:1 to open label treatment with three insulin analogue regimens: biphasic insulin aspart one to three times daily versus insulin aspart three times daily in combination with insulin detemir once daily versus insulin detemir once daily (see online supplementary figure S1).[16] Participants, investigators and medical staff were blinded to the intervention with metformin or placebo (numbered containers). Randomisation was stratified by age >65 years, insulin at trial entry and treatment at the Steno Diabetes Center (recruiting half of the participants).

The protocol was approved by the Regional Committee on Biomedical Research Ethics (H-D-2007-112) and the Danish Medicines Agency, registered within ClinicalTrials.gov (NCT00657943), and conducted in accordance with The Declaration of Helsinki and guidelines for Good Clinical Practice.

Intervention, visits and investigations

After local screening, ultrasound of the carotid arteries and clinical investigations were performed in eligible participants at the Steno Diabetes Center. All participants, in whom it was possible to analyse carotid IMT, were subsequently randomised at their local diabetes clinic and all prior antihyperglycaemic drugs were discontinued. Participants treated with metformin before trial entry initiated a dose of metformin/placebo of 1 g twice daily. Participants not treated with metformin before trial entry were titrated from 500 mg once daily to 1 g twice daily during 4 weeks. The dose was reduced to the maximal tolerated dose in case of intolerance. Initiation and titration of insulin treatment is described elsewhere.[16] Independent of the treatment group, investigators aimed at a HbA_{1c} ≤7.0% (≤53 mmol/mol). Participants were treated with antihypertensives and statins according to guidelines and received aspirin 75 mg/day at the discretion of the investigators.

Every third month, participants were examined at their local diabetes clinic (clinical examinations, fasting blood samples, registration of adverse events and hypoglycaemic episodes and adjustments of medications). After 18 months of intervention, investigations at trial entry were repeated and trial medication was subsequently terminated at the local diabetes clinic.

Measurement of carotid IMT was performed by the same two technicians in all participants using General Healthcare logic 9 for the ultrasound scan and specialised software for the analyses. First, plaques or stenoses were identified in the left and right bifurcation, common and internal carotid artery and quantified 0–5 (if there were more than five plaques, it was calculated as five). Subsequently, carotid IMT was measured in the far wall of the common carotid artery 10 mm proximal to the bulb and averaged from the left and right sides. The technicians were blinded with respect to the metformin versus placebo comparison. Regarding insulin, the technicians were not informed about the treatment group. However, we cannot exclude that occasional information about which insulin analogue the participant used was given to the technician. A detailed description of the carotid ultrasound protocol can be found in online supplementary appendix 2. Methodology and reproducibility have been reported previously.[13 17]

Outcomes

The primary outcome was change in mean carotid IMT of the common carotid arteries. Secondary outcomes reported here were hypoglycaemia and serious adverse events. Other pre-specified explorative outcomes were changes in maximal carotid IMT, number of atherosclerotic plaques, glycaemic control (HbA_{1c}, fasting plasma glucose, insulin and C-peptide), insulin dose and body composition. In the analysis plan finalised and accepted by all investigators before data lock, carotid intima-media area, relative compliance and incremental elastic modulus were included as explorative outcomes. Other prespecified explorative outcomes will be reported separately.[17]

Statistical analyses

Sample size calculation was based on an α value of 0.01 to allow for five major comparisons between intervention groups.[17] Thus, 900 participants were needed to detect a minimal relevant difference of 0.018 mm in carotid IMT between metformin and placebo during 18 months with statistical power of 85%, assuming a population SD of 0.075 mm, similar to the effect reported in a meta-analysis of statins, for proving or refuting the primary hypothesis of metformin being able to reduce the progression of carotid IMT compared with placebo.[17 18] Whenever possible, participants who discontinued trial medication before 18 months came to a final measurement of carotid IMT. Missing data on the primary outcome were imputed using multiple imputation.[19] The primary analysis was intention-to-treat of the mean carotid IMT at 18 months adjusted for stratification variables and baseline value of carotid IMT. Secondary analyses were adjusted only for baseline value. Analysis of explorative outcomes were conducted by a random effects model for all observations, with a random person effect, including stratification variables and design variables (sex, prior cardiovascular disease, statin treatment and positive glutamic acid decarboxylase antibodies). This model was also used for reporting the changes in mean carotid IMT in each randomisation group, as these changes are not modelled in the specified primary analysis with baseline control.

The primary analysis was protocolised with adjustment only for baseline values. However, adjustment for stratification variables has recently been recommended to preserve power in stratified randomised trials.[20] Further, a per protocol analysis was performed (exclusion of participants not fulfilling the criteria for participation, never receiving the allocated trial medication or having major deviations to the protocol (not meeting to at least four visits).[21] The statistical model used for analysis of hypoglycaemic events was a Poisson model for the rate of events for each person and a logistic regression for occurrence of any event. We did not plan to adjust predefined analyses for multiplicity. However, to adjust for multiplicity, we calculated that the significance level be adjusted to 0.05/(K+1)/2 (where K represents the number of prespecified secondary outcomes).[22]

All analyses were made in the statistical programme R. (R Core Team (2013).

RESULTS

Anonymised participant level data and a detailed account of all statistical analyses can be found at http://bendixcarstensen.com/SDC/CIMT/DOM/CIMT.pdf

Trial participants

Four hundred and fifteen of the 464 persons assessed for eligibility met the criteria for participation and were randomly allocated to metformin versus placebo, all in combination with one of three insulin analogue regimens (flow diagram attached as figure 1). Owing to server failure during the trial, the randomisation code was lost for three participants, who were therefore excluded from the analyses. Thus, 206 participants were allocated to metformin in combination with insulin (metformin group). Thirty-one participants did not complete intervention resulting in 175 (85%) completers. Fifteen non-completers returned for the last visit. Similarly, 206 participants were allocated to placebo in combination with insulin (placebo group), while 49 participants discontinued intervention resulting in 157 (76%) completers. Twenty-eight non-completers returned for the last visit. The number of completers was significantly higher in the metformin group compared with the placebo group (p=0.03). More patients in the placebo group dropped out due to hyperglycaemia or hypoglycaemia (figure 1). The participants were well matched at entry, with a mean age of 60–61 years and a mean duration of diabetes of 12–13 years, and 69% of the participants received insulin prior to trial participation (table 1).

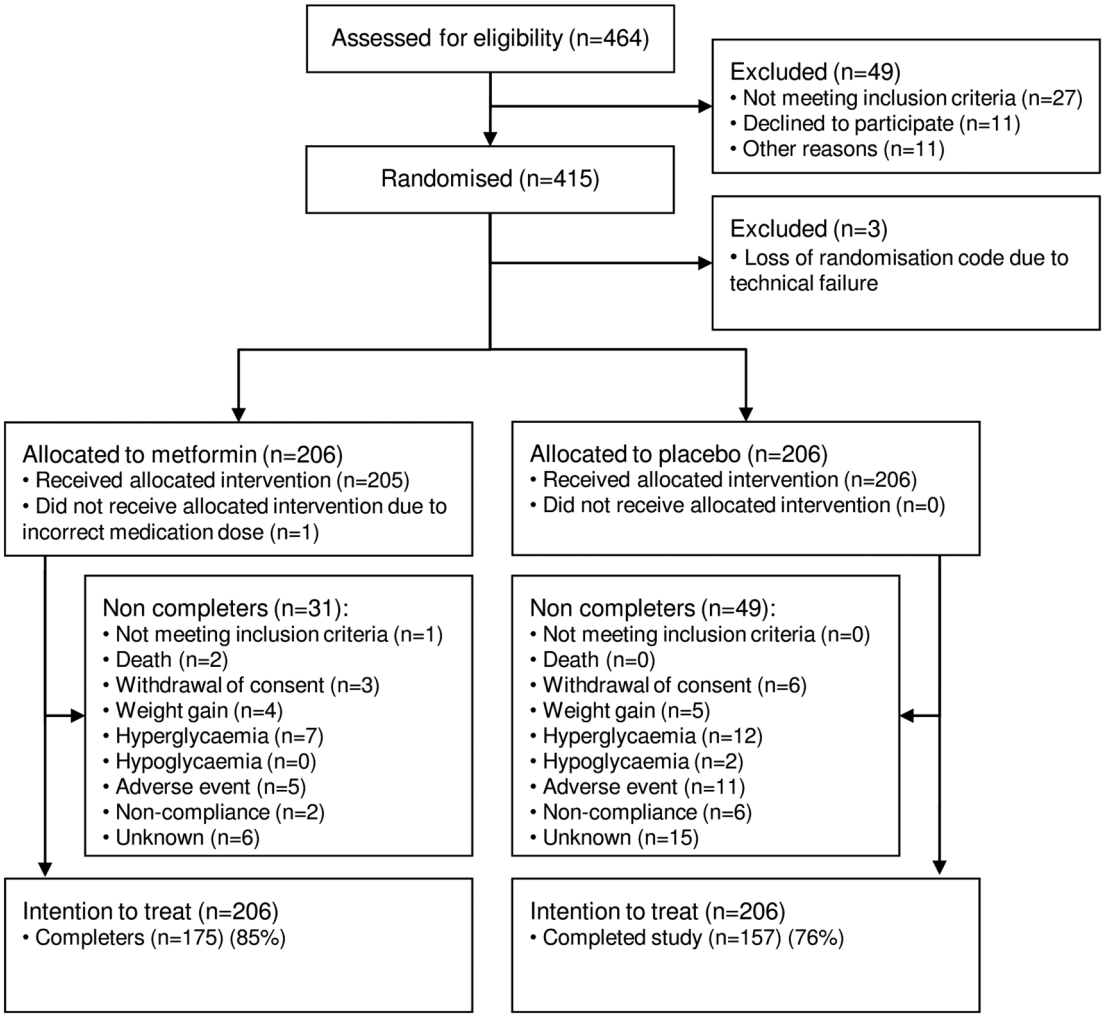

Figure 1 Flow of participants through trial.

Change in carotid IMT and other ultrasound-derived variables

Change in mean carotid IMT did not differ between the metformin and placebo groups (mean between-group difference 0.012 mm (95% CI −0.003 to 0.026), p=0.11, figure 2 and table 2). Mean carotid IMT did not change in the metformin group (−0.001 mm (95% CI −0.011 to 0.010), p=0.88), whereas a significant reduction was observed in the placebo group (−0.014 mm (95% CI −0.024 to −0.003), p=0.011). The interaction with the insulin regimens did not reach statistical significance (p=0.085, http://bendixcarstensen.com/SDC/CIMT/DOM/CIMT.pdf). Maximal carotid IMT was likewise significantly reduced in the placebo group by −0.014 mm (95% CI −0.026 to −0.002), p=0.03 without significant between group differences (p=0.19, table 2). No between-group differences were observed with regard to intima-media area, relative compliance and incremental elastic modulus (data not shown). The number of plaques increased in both groups without a between-group difference (data not shown).

Glycaemic control, weight and insulin doses

HbA_{1c} was more reduced in the metformin group (−0.78% (95% CI −0.92% to −0.64%) (−8.5 mmol/mol (95% CI −10.1 to −7.0))) compared with the placebo group (−0.36% (95% CI −0.50% to −0.22%) (−3.9 mmol/mol (95% CI −5.5 to −2.4))), between-group difference −0.42% (95% CI −0.62% to −0.23%) (−4.6 mmol/mol (95% CI −6.8 to −2.5)), p<0.001 (table 2). HbA_{1c} level at end of trial was lower in the metformin group compared with the placebo group, p=0.006 (table 2). Fasting plasma glucose, C-peptide and insulin levels were reduced in both groups without significant between-group differences (table 2 and figure 3). The variables p-insulin, C-peptide, insulin dose, very low-density lipoprotein cholesterol and triglycerides did not meet the criteria of a normal distribution and were accordingly log transformed. Therefore, these variables are presented in table 2 with relative change from baseline instead of absolute change.

Participants in the metformin group experienced a less pronounced weight gain (1.6 kg (95% CI 1.1 to 2.1) compared with the placebo group (4.2 kg (95% CI 3.6 to 4.7), p<0.001).

Table 1 Baseline characteristics of participants by allocation group

	Metformin +insulin (n=206)	Placebo +insulin (n=206)
Age (years)	61.0 (8.7)	60.3 (9.1)
Male, N (%)	140 (68)	141 (68)
Weight (kg)	97.2 (15.2)	97.1 (14.7)
Body mass index*	32.3 (4.2)	32.1 (4.2)
Waist-hip ratio	1.00 (0.08)	1.01 (0.08)
Smokers, N (%)	36 (18)	27 (13)
Median (IQR) alcohol consumption (units/week)	2 (0–6)	1 (0–5)
Caucasians, N (%)	201 (98)	201 (98)
Diabetes and complications		
Duration of type 2 diabetes (years)	13.5 (6.2)	12.2 (6.5)
GAD65 antibodies ≥25 U/mL, N (%)	19 (9)	11 (5)
HbA_{1c} (%)	8.6 (1.1)	8.5 (1.0)
HbA_{1c} (mmol/mol)	70 (12)	69 (11)
Fasting p-glucose (mmol/L)	10.5 (3.3)	10.1 (3.2)
Median (IQR) fasting p-insulin (pmol/L)	65 (37–107)	73 (44–128)
Median (IQR) fasting c-peptide (pmol/L)	746 (451–1186)	861 (484–1257)
Prior cardiovascular disease, N (%)†	45 (22)	55 (27)
Microalbuminuria, N (%)	48 (24)	40 (20)
Macroalbuminuria, N (%)	12 (6)	8 (4)
eCCr‡ (mL/min)	130 (44)	126 (45)
Simple retinopathy, N (%)	59 (30)	63 (31)
Proliferative retinopathy, N (%)	15 (8)	10 (5)
Prior laser treatment, N (%)	21 (10)	16 (8)
Autonomous neuropathy, N (%)	33 (16)	36 (18)
Peripheral neuropathy, N (%)	76 (37)	78 (38)
Blood pressure and lipids		
Systolic blood pressure (mm Hg)	141.5 (15.1)	138.2 (15.5)
Diastolic blood pressure (mm Hg)	82.2 (9.4)	82.0 (9.2)
Heart rate (bpm)	76.0 (12.0)	76.7 (11.8)
Total cholesterol (mmol/L)	4.2 (1.0)	4.1 (0.9)
LDL cholesterol (mmol/L)	2.2 (0.8)	2.2 (0.8)
Median (IQR) VLDL cholesterol (mmol/L)	0.8 (0.5–1.0)	0.7 (0.5–0.9)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.4)
Median (IQR) triglycerides (mmol/L)	1.7 (1.2–2.3)	1.5 (1.1–2.1)
Medication		
Metformin, N (%)§	167 (81)	176 (86)
Insulin, N (%)§	143 (69)	142 (69)
Sulfonylurea, N (%)§	61 (30)	55 (27)
Other antihyperglycaemic drug, N (%)§	32 (16)	27 (13)
RAS blockade, N (%)	159 (77)	149 (72)
Other antihypertensive drug, N (%)	122 (59)	111 (54)
Statin, N (%)	170 (83)	181 (88)
Aspirin, N (%)	112 (54)	119 (58)
Carotid ultrasound measures		
Mean carotid IMT (mm)	0.788 (0.135)	0.799 (0.139)
Maximal carotid IMT (mm)	0.953 (0.151)	0.959 (0.156)
Relative compliance $\times 10^3$ ($mmHg^{-1}$)	2.5 (1.1)	2.6 (1.0)
Incremental elastic modulus (mm Hg)	2387 (978)	2307 (1080)
Carotid intima-media area (mm^2)	18.9 (4.7)	19.4 (4.8)
Median (IQR) number of plaques¶	3 (1–4)	3 (2–5)

Values are means (SDs) unless stated otherwise.
*Body mass index is calculated as weight (kg) divided by height $(m)^2$.
†Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, vascular surgery, stroke, transitory cerebral ischaemia, amputation.
‡Calculated by the Cockcroft Gault equation: eCCr=((140-age)×weight (kg)×constant)/serum creatinine (micromol/L), constant female: 1.04, male: 1.23.
§All antihyperglycaemic drugs were terminated at randomisation.
¶Sum of plaques in left and right bifurcation, common and internal carotid artery.
CVD, cardiovascular disease; eCCr, estimated creatinine clearance; GAD, glutamic acid decarboxylase; HbA_{1c}, haemoglobin A_{1c}; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; RAS, Renin angiotensin system; VLDL, very low-density lipoprotein.

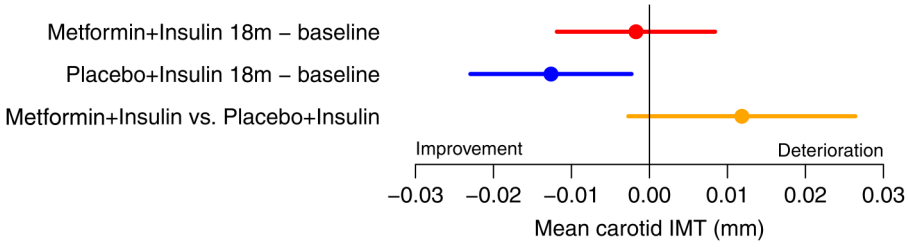

Figure 2 Changes in the mean carotid intima-media thickness (IMT) (mean (95% CI)) in the metformin+insulin group (red), placebo+insulin group (blue) group, and the intervention effect (yellow) from the random effects model with baseline as the covariate using multiply imputed data, adjusted for stratification variables.

Insulin doses increased in both groups during the trial (table 2 and figure 3), but were smaller in the metformin group at end of trial (1.04 IU/kg (95% CI 0.94 to 1.15) compared with the placebo group (1.36 IU/kg (95% CI 1.23 to 1.51), p<0.001). An insulin dose represents the dose prescribed by the investigator at each visit for the following three months, hence the last insulin dose registered is at 15 months (figure 3), being the last dose prescribed for the last three months in the trial.

Hypoglycaemia and serious adverse events

The groups did not differ in the number of participants experiencing at least one episode of severe hypoglycaemia (seven in both groups) or in the total number of severe hypoglycaemic episodes (15 vs 12, table 3).[23] The number of participants experiencing at least one episode of non-severe hypoglycaemia were also similar (157 vs 156) in both groups, whereas the metformin group had a higher total number of non-severe hypoglycaemic episodes (4347) compared with the placebo group (3161, p<0.001). Eighty-one serious adverse events were reported in 54 participants in the metformin group compared with 72 serious adverse events in 45 participants in the placebo group without significant difference between the groups (table 3 and see online supplementary material tables S1 and S2).

Blood pressure and lipids

Blood pressures were significantly reduced in both groups with no between-group difference. The heart rate decreased significantly in the placebo group compared with the metformin group (p=0.010, table 2).

Total cholesterol level remained unchanged in the metformin group but increased significantly in the placebo group (table 2). Likewise, LDL cholesterol level increased significantly in the placebo group (p<0.001) with a between-group difference of −0.18 mmol/L (95% CI −0.31 to −0.04), p=0.010, table 2.

The prespecified sensitivity analyses described above did not noticeably change the results (analyses available at http://bendixcarstensen.com/SDC/CIMT/DOM/CIMT.pdf).

DISCUSSION

Intervention with metformin in combination with insulin did not reduce carotid IMT despite the larger reduction in HbA_{1c}, less weight gain, and smaller insulin dose compared with placebo in combination with insulin in patients with type 2 diabetes. Surprisingly, carotid IMT was reduced (suggesting a reduction in cardiovascular risk) during the 18 months treatment with insulin alone, despite a significant increase in total and LDL cholesterol levels and body weight. In contrast, carotid IMT did not change in participants treated with insulin in combination with metformin.

The results did not support our a priori hypothesis of a beneficial effect of −0.018 mm on the progression of carotid IMT in favour of metformin in combination with insulin compared with insulin alone. On the contrary, our data are compatible with an alternative hypothesis in favour of insulin alone compared with metformin in combination with insulin, since 0.018 mm is included in the 95% CI of the between group difference.

Only a few previous studies have examined the effect of metformin on carotid IMT in patients with type 2 diabetes. Stocker *et al* found a significant improvement in maximal carotid IMT of −0.037 mm (p=0.02) in 92 participants randomised to rosiglitazone compared with metformin despite equal improvement in glycaemic control.[24] In contrast, two small unblinded studies reported improvements in carotid IMT progression in participants receiving metformin.[25 26] The recently published CAMERA trial found no significant effect of 18 months treatment with metformin versus placebo on mean carotid IMT in 173 participants without diabetes with established cardiovascular disease.[27] While the results regarding the effect of metformin have been conflicting, more consistent beneficial effects on progression of carotid IMT have been found during α-glucosidase inhibitors or pioglitazone treatments.[28 29]

Despite aiming at the same glycaemic target (HbA_{1c} ≤7.0% (≤53 mmol/mol)) in all participants, HbA_{1c} was significantly more reduced in the metformin group, even though the participants received significantly smaller amounts of insulin compared with the placebo group. The placebo group experienced a more pronounced weight gain, probably as a consequence of the increased insulin dose and the absent anorectic effect of

Table 2 Changes in outcomes from trial entry to 18 months*

	Metformin+insulin (n=206)	Placebo+insulin (n=206)	Metformin vs placebo	p Value
Carotid ultrasound measures				
Mean carotid IMT (mm)†	−0.001 (−0.011 to 0.010)	−0.014 (−0.024 to −0.003)	0.012 (−0.003 to 0.026)	0.1105
Maximal carotid IMT (mm)	−0.003 (−0.015 to 0.010)	−0.014 (−0.026 to −0.002)	0.011 (−0.006 to 0.029)	0.1943
Body composition				
Weight (kg)	1.6 (1.1 to 2.1)	4.2 (3.6 to 4.7)	−2.6 (−3.3 to −1.8)	<0.001
Body mass index (kg/m^2)	0.45 (0.28 to 0.63)	1.36 (1.19 to 1.54)	−0.91 (−1.16 to −0.66)	<0.001
Waist-hip ratio	0.01 (0.00 to 0.02)	0.00 (−0.01 to 0.01)	0.01 (−0.01 to 0.02)	0.2834
Glycaemic control				
HbA_{1c} (%)	−0.78 (−0.92 to −0.64)	−0.36 (−0.50 to −0.22)	−0.42 (−0.62 to −0.23)	<0.001
HbA_{1c} (mmol/mol)	−8.5 (−10.1 to −7.0)	−3.9 (−5.5 to −2.4)	−4.6 (−6.8 to −2.5)	<0.001
HbA_{1c} at 18 months (%)	7.97 (7.78 to 8.16)	8.27 (8.08 to 8.47)	−0.31 (−0.52 to −0.09)	0.0063
HbA_{1c} at 18 months (mmol/mol)	64 (62 to 66)	67 (65 to 69)	−3.4 (−5.7 to −1.0)	0.0063
Participants with HbA_{1c}≤7.0% at end of trial, N (%)	53 (26)	28 (14)		0.0038
Fasting p-glucose (mmol/L)	−2.14 (−2.64 to −1.64)	−1.67 (−2.18 to −1.16)	−0.47 (−1.18 to 0.25)	0.2008
Fasting p-insulin (relative change from baseline)	0.67 (0.58 to 0.77)	0.63 (0.54 to 0.73)	107% (87% to 131%)	0.5312
Fasting C-peptide (relative change from baseline)	0.73 (0.67 to 0.80)	0.69 (0.63 to 0.75)	106% (94% to 120%)	0.3477
Insulin dose at end of trial (IU/day/kg)	1.04 (0.94 to 1.15)	1.36 (1.23 to 1.51)	76% (68% to 86%)	<0.001
Insulin dose at end of-trial (IU/day)	102 (91 to 115)	138 (123 to 155)	74% (65% to 84%)	<0.001
Insulin dose (relative change from baseline)	2.13 (2.00 to 2.26)	2.82 (2.64 to 3.01)	75% (69% to 83%)	<0.001
Blood pressure and lipids				
Systolic blood pressure (mm Hg)	−5.7 (−8.0 to −3.4)	−5.4 (−7.7 to −3.0)	−0.3 (−3.6 to 2.9)	0.8434
Diastolic blood pressure (mm Hg)	−3.5 (−4.8 to −2.3)	−3.0 (−4.2 to −1.7)	−0.6 (−2.3 to 1.2)	0.5383
Heart rate (bpm)	−0.3 (−1.7 to 1.1)	−3.0 (−4.4 to −1.5)	2.7 (0.6 to 4.7)	0.0100
Total cholesterol (mmol/L)	0.07 (−0.04 to 0.18)	0.20 (0.09 to 0.32)	−0.13 (−0.29 to 0.03)	0.1089
LDL cholesterol (mmol/L)	0.04 (−0.06 to 0.13)	0.21 (0.12 to 0.31)	−0.18 (−0.31 to −0.04)	0.0101
VLDL cholesterol (relative change from baseline)	1.02 (0.96 to 1.08)	0.97 (0.92 to 1.03)	104% (96% to 113%)	0.3042
HDL cholesterol (mmol/L)	0.01 (−0.02 to 0.04)	0.00 (−0.03 to 0.02)	0.02 (−0.03 to 0.06)	0.4577
Triglycerides (relative change from baseline)	1.01 (0.95 to 1.07)	0.98 (0.93 to 1.04)	103% (95% to 112%)	0.4735

The variables p-insulin, C-peptide, insulin dose, VLDL cholesterol and triglycerides did not meet the criteria of a normal distribution and were accordingly log transformed. Therefore, these variables are presented with relative change from baseline instead of absolute change.
To adjust for multiplicity, the significance level can be adjusted to 0.05/(K+1)/2 (where K represents the number of prespecified secondary outcomes) equalling in this case an α=0.0045.
HbA_{1c}, haemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
*Intention to treat, mixed model analyses with random effect person adjusted for stratification variables, results are presented as mean (95% CI).
†Between group differences are analysed using multiple imputation of missing values.

metformin.[30] The effects of metformin on HbA_{1c}, weight and insulin dose are in accordance with the Hyperinsulinaemia: the Outcome of Its Metabolic Effects (HOME) trial, in which glycaemic goals were also identical for both the metformin plus insulin and the insulin only groups. The achieved absolute reduction in HbA_{1c} in the metformin group in our trial was 0.8% compared to 0.4% in the HOME trial, demonstrating the difficulties in obtaining HbA_{1c} reductions despite high insulin doses in these groups of patients with a long duration of diabetes.[8] A recent systematic review of metformin in combination with insulin as compared with insulin alone reported significantly lower HbA_{1c}, weight gain and insulin dose, but no evidence of reduced risk of cardiovascular disease.[11] However, the review reports a marked paucity of data,

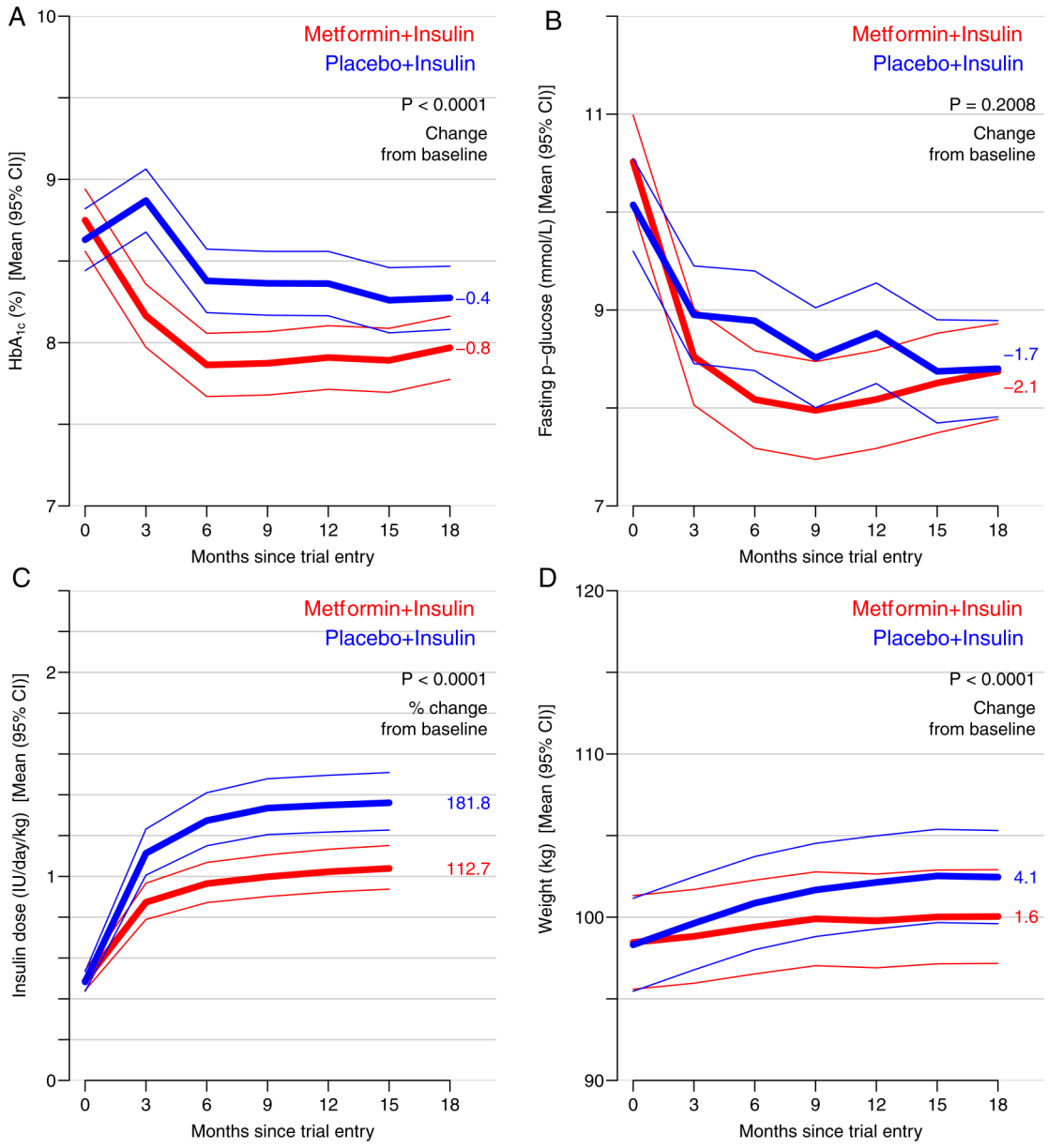

Figure 3 Changes (mean (95% CI)) during 18 months of intervention with metformin+insulin (red) and placebo+insulin (blue) in HbA_{1c} (A), fasting plasma glucose (B), insulin dose (C), and weight (D). Numbers on the right-hand side of the graphs indicate the absolute/relative changes from trial entry to end of trial.

making it difficult to reach robust conclusions, which underscores the need for a more comprehensive knowledge on the cardiovascular effects of metformin.[11] The HOME trial randomised 390 insulin treated patients with type 2 diabetes to either adjunct metformin or placebo and reported improvement in the secondary composite macrovascular outcome with metformin. However, the p value was marginal (p=0.04) and the analysis was adjusted for baseline differences while not reported if prespecified; thus, the analyses may rather be the result of a post hoc analysis.[8] Importantly, recent meta-analyses have also challenged the conclusion from the UKPDS of improved cardiovascular outcomes with metformin monotherapy compared with insulin secretagogues in type 2 diabetes.[10 12] Furthermore, random allocation to combination therapy with metformin plus sulfonylureas was associated with increased mortality compared with sulfonylureas alone in UKPDS, a finding supported by recent meta-analyses,[9 12 31] whereas a large observational study suggests that adding sulfonylurea to metformin may improve clinical outcomes compared to addition of insulin.[32]

Strengths and limitations

Strengths of the CIMT trial include the centrally randomised, placebo-controlled blinded design and the relatively large population of well-characterised patients.[33 34]

Table 3 Hypoglycaemia and serious adverse events during 18 months of intervention

	Metformin+insulin (n=206)	Placebo +insulin (n=206)	p Value
Severe hypoglycaemia (number of participants with at least one event, N (%))	7 (3.4)	7 (3.4)	0.9958
Severe hypoglycaemia (number of events (rate among participants with at least one event))	15 (2.1)	12 (1.7)	0.5654
Non-severe hypoglycaemia (number of participants with at least one event, No (%))	157 (76.2)	156 (75.7)	0.9374
Non severe hypoglycaemia (number of events (rate among participants with at least one event))	4347 (27.7)	3161 (20.3)	<0.001
Serious adverse events exclusive of severe hypoglycaemia (number of participants with at least one event, N (%))	54 (26.2)	45 (21.8)	0.3173
Serious adverse events exclusive of severe hypoglycaemia (number of events (rate among participants with at least one event))	81 (1.5)	72 (1.6)	0.5029

Severe hypoglycaemia defined as a hypoglycaemic episode where help from a third person was needed. Non-severe hypoglycaemia defined as an episode with either symptoms of hypoglycaemia and/or measurement of plasmaglucose ≤3.9 mmol/L.

All ultrasound scans were performed by the same two technicians using automated software with good reproducibility.[13] A limitation is the choice of carotid IMT as a surrogate risk marker for cardiovascular disease instead of using clinical hard outcomes. We cannot exclude any long-term effects beyond the 18 months of intervention. Carotid IMT has been shown to be strongly predictive of future cardiovascular disease, but the ability to accurately predict future cardiovascular disease from a change in carotid IMT remains unproven.[14 35] Ideally, our trial should have been based on clinical hard outcomes, but this would have required a much higher number of participants, which was not possible in this investigator initiated trial. Caused by reduced inclusion rates, which to some extent may be explained by a sustained strike among nurses, the introduction of liraglutide as a competing treatment option and/or concerns about reduced glucose lowering efficacy of detemir in some type 2 diabetes patients, we were only able to include approximately half of the participants originally planned for in this trial However, our sample size estimation was conservative using an α of 0.01 and a power of 85%, resulting in a twofold to fourfold higher estimated number of participants as compared to several other trials having carotid IMT as the primary outcome: the ongoing REMOVAL trial (NCT01483560) investigates the effect of metformin versus placebo in 500 patients with type 1 diabetes with mean carotid IMT as the primary outcome, and the CAMERA trial estimated a sample size of 180 participants to investigate the effect of metformin versus placebo in non-diabetic people with established cardiovascular disease.[27] Furthermore, in the perspective of the observed and somewhat paradoxical carotid IMT changes in our trial in favour of insulin alone, it appears unlikely that the results, even with the inclusion of 900 participants, could have supported our a priori hypothesis of metformin in combination with insulin being superior to placebo in combination with insulin with regard to changes in carotid IMT.

CONCLUSIONS

In conclusion, despite the larger reduction in HbA_{1c}, less weight gain and smaller insulin dose, we found no beneficial effect of 18 months treatment with metformin in combination with insulin on mean carotid IMT—a risk marker of cardiovascular disease—compared with placebo in combination with insulin in patients with type 2 diabetes. Our results question the cardiovascular effects of the internationally recommended combination of metformin and insulin as compared with insulin alone. It has been discussed whether further metformin trials in type 2 diabetes would be ethical (http://www.easdvirtualmeeting.org/resources/6795). The paucity of evidence strongly suggests that such trials are warranted, including trials focusing on the combination of metformin with insulin. In addition, metformin has been used for decades, but the mechanisms of the cardiometabolic effects of metformin, if any, remain to be elucidated.[36 37]

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Contributors All authors (except BC) contributed to the design, conduct and acquisition of data. LL-C and BC conducted the data analysis, tables and figures. LL-C, BC, LT, TPA, AV, JW, CG and SM drafted the manuscript and conducted interpretation of data. All authors had full access to all the data and statistical reports in the trial and can take responsibility for the integrity of the data and the accuracy of the data analysis. They revised and approved the final version of the manuscript. LL-C and BC affirm as the guarantors that the manuscript is an honest, accurate and transparent account of the trial, and that no important aspects of the trial have been omitted.

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Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: the trial received an unrestricted grant from Novo Nordisk A/S for the submitted work; LL-C, LT, TPA, AV, OP, TWB, BC, SSL and TJ have reported shares in Novo Nordisk A/S; LL-C, LT, TPA, AV, TWB and SSL have reported former employment and BC is employed at Steno Diabetes Center, which is a diabetes hospital and academic institution owned by Novo Nordisk; SSL owns shares in dynamically traded investment funds, which may own stocks from pharmaceutical companies; SSL is employed at Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; SSL's contribution was his alone and does not necessarily reflect the official position of Boehringer Ingelheim; AV has received fees from Novo Nordisk; TWB is employed at Novo Nordisk A/S; BT is a member of the advisory board for Eli Lilly; OS has received fees from AstraZeneca, Sanofi, MSD, Boehringer-Ingelheim, Eli Lilly and NovoNordisk; CH has received fees from Bristol-Myers Squibb; LB has received fees from and has attended as advisor for Novo Nordisk A/S; SM has served as a consultant or adviser to: Novartis Pharma, Novo Nordisk, Merck Sharp & Dome, Sanofi-Aventis, AstraZeneca, Johnson & Johnson, Rosche, Mankind, Astra-Zeneca, Boehringer-Ingelheim, Zeeland, E Lilly, Intarcia Therapeutics and Bristol-Meyer Squibb; he has received fee for speaking from Novo Nordisk, Merck, Sharp & Dome, Astra-Zeneca, Johnson and Johnson, Rosche, Shering-Ploug, Sanofi-Aventis, Novartis Pharma, E Lilly, Bristol-Meyer Squibb and Boehringer Ingelheim, and has received 2 research grants from Novo Nordisk. BH, BG-R, JW, CG, NW, MR, HV, ED, HP, TK, SBS and ERM have no conflicts of interests to declare.

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