

# BMJ Open Effects of biphasic, basal-bolus or basal insulin analogue treatments on carotid intima-media thickness in patients with type 2 diabetes mellitus: the randomised Copenhagen Insulin and Metformin Therapy (CIMT) trial

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## ABSTRACT

**Objective:** To assess the effect of 3 insulin analogue regimens on change 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 8 hospitals in Denmark.

**Participants and interventions:** Participants with type 2 diabetes (glycated haemoglobin (HbA<sub>1c</sub>) ≥7.5% (≥58 mmol/mol), body mass index >25 kg/m<sup>2</sup>) were, in addition to metformin versus placebo, randomised to 18 months open-label biphasic insulin aspart 1–3 times daily (n=137) versus insulin aspart 3 times daily in combination with insulin detemir once daily (n=138) versus insulin detemir alone once daily (n=137), aiming at HbA<sub>1c</sub> ≤7.0% (≤53 mmol/mol).

**Outcomes:** Primary outcome was change in mean carotid IMT (a marker of subclinical cardiovascular disease). HbA<sub>1c</sub>, insulin dose, weight, and hypoglycaemic and serious adverse events were other prespecified outcomes.

**Results:** Carotid IMT change did not differ between groups (biphasic −0.009 mm (95% CI −0.022 to 0.004), aspart+detemir 0.000 mm (95% CI −0.013 to 0.013), detemir −0.012 mm (95% CI −0.025 to 0.000)). HbA<sub>1c</sub> was more reduced with biphasic (−1.0% (95% CI −1.2 to −0.8)) compared with the aspart +detemir (−0.4% (95% CI −0.6 to −0.3)) and detemir (−0.3% (95% CI −0.4 to −0.1)) groups (p<0.001). Weight gain was higher in the biphasic (3.3 kg (95% CI 2.7 to 4.0)) and aspart+detemir (3.2 kg (95% CI 2.6 to 3.9)) compared with the detemir group (1.9 kg (95% CI 1.3 to 2.6)). Insulin dose was higher with detemir (1.6 IU/kg/day (95% CI 1.4 to 1.8)) compared with

## Strengths and limitations of this study

- It is not known to what extent different insulin analogue regimens primarily targeting basal or postprandial hyperglycaemia may influence the risk of cardiovascular disease in a differential manner 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 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 hard clinical outcomes.
- The trial only reached 46% of the planned sample size and lack of power may therefore have affected our results.

biphasic (1.0 IU/kg/day (95% CI 0.9 to 1.1)) and aspart +detemir (1.1 IU/kg/day (95% CI 1.0 to 1.3)) (p<0.001). Number of participants with severe hypoglycaemia and serious adverse events did not differ.

**Conclusions:** Carotid IMT change did not differ between 3 insulin regimens despite differences in HbA<sub>1c</sub>, weight gain and insulin doses. The trial only reached 46% of planned sample size and lack of power may therefore have affected our results.

**Trial registration number:** NCT00657943.

## INTRODUCTION

Intensified treatment with insulin eventually becomes necessary to maintain acceptable glycaemic control in most patients with type 2 diabetes (T2D),<sup>1</sup> although this intervention has not been proven to reduce the risk of cardiovascular disease.<sup>2,3</sup> Insulin regimens targeting postprandial glucose excursions may reduce risk of atherosclerosis compared with regimens primarily targeting fasting glucose levels.<sup>4,5</sup> Clinical guidelines have endorsed use of basal insulin preparations as the preferential initial insulin regimen.<sup>1</sup> This recommendation is based on reports indicating that use of basal bedtime insulin may be associated with less weight gain and reduced risk of hypoglycaemia.<sup>6–8</sup> Nevertheless, treatment with basal insulin may be insufficient, and addition of rapid-acting insulin before meals (basal-bolus therapy) or switching to one or more daily injections of premixed insulin preparations may become necessary to reduce and maintain the glycated haemoglobin (HbA<sub>1c</sub>) targets.<sup>6,9–13</sup> However, large-scale long-term (>12 months) comparisons to guide the clinician's choice between the different insulin regimens are lacking.

Carotid intima-media thickness (IMT) is a risk marker for cardiovascular disease, and has been shown to correlate with established—and to predict future—cardiovascular disease.<sup>14–16</sup>

The objective of the Copenhagen Insulin and Metformin Therapy (CIMT) trial was to evaluate the effect of 18 months intervention with metformin versus placebo in combination with three insulin analogue regimens on the progression of mean carotid IMT in patients with T2D. The metformin versus placebo comparison was defined as the primary objective and reported in a separate article in this volume of *BMJ Open*,<sup>17</sup> whereas comparisons between insulin regimens were defined as secondary objectives and reported in this article.

## MATERIALS AND METHODS

### Trial design, participants and randomisation

The CIMT trial is an investigator-initiated, multicentre, randomised superiority trial with a 2×3 factorial design, conducted from May 2008 to December 2012, as previously described.<sup>17,18</sup> Participants with T2D, age >30 years, body mass index (BMI) >25 kg/m<sup>2</sup>, HbA<sub>1c</sub> ≥7.5% (58 mmol/mol), treated with oral antidiabetic drugs for at least 1 year and/or insulin treatment for at least 3 months, where the investigator deemed the patient capable of insulin therapy once daily, were recruited from the eight diabetes outpatient clinics in the Capital Region, Denmark. 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 birth control measure and allergy towards trial medication. All participants gave written informed

consent before participation and, after a screening visit, were centrally randomised according to the 2×3 factorial design. Randomisation was, in the first step, performed according to a computer-generated allocation sequence, 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 two steps, randomised 1:1:1 to one of three insulin analogue regimens and 1:1 to treatment with metformin versus placebo (see online supplementary figure S1). Randomisation was stratified by age >65 years, insulin treatment at trial entry and treatment at Steno Diabetes Center (recruiting half of the participants). The insulin treatment was open-labelled, whereas participants, investigators and medical staff were blinded to the metformin or placebo intervention.

### Intervention, visits and investigations

After local screening and investigations including analysis of carotid IMT at Steno Diabetes Center, prior glucose lowering drugs were discontinued, and participants initiated allocated treatment with one of three insulin regimens: biphasic insulin aspart before main meals one to three times daily (biphasic group) versus insulin aspart before main meals three times daily in combination with bedtime insulin detemir once daily (aspart+detemir group) versus bedtime insulin detemir alone once daily (detemir group), all in combination with metformin 1 g two times daily versus matching placebo (Ref. 17 and see online supplementary figure S1). In all treatment groups, the aim was HbA<sub>1c</sub> ≤7.0% (≤53 mmol/mol). Participants treated with insulin before trial entry were allocated insulin at a daily dose similar to the pretrial dose. Participants not treated with insulin before trial entry were initiated with a daily insulin dose of 0.2 IU/kg. The insulin dose was continuously titrated based on fasting, and preprandial and postprandial plasma glucose levels, with guidance from an insulin titration algorithm (see online supplementary appendix 1). A proportion of participants randomised to detemir once daily experienced unacceptably high blood glucose excursions despite high detemir doses. The degree of this challenge was not expected prior to the trial and it was therefore necessary to make an amendment to the protocol during the trial, which was approved by the Regional Committee on Biomedical Research Ethics by 1 July 2009. The participants were thereafter supplemented with a morning dose of detemir if HbA<sub>1c</sub> ≤7.0% was not reached and plasma glucose levels in the evening were >10 mmol/L despite acceptable fasting plasma glucose levels (4.4–6.1 mmol/L). If acceptable glycaemic response (defined as HbA<sub>1c</sub> ≤7.0% or a reduction in HbA<sub>1c</sub> of 0.5%) was reached after 3–6 months, twice daily detemir was continued, otherwise treatment was changed to detemir once daily in combination with insulin aspart before one or more meals. Participants were treated with antihypertensives and statins according to guidelines and

received aspirin 75 mg/day at the discretion of the investigators.

During the 18-month intervention, participants were seen every third month at their local diabetes clinics. Before termination of trial medication, investigations including carotid IMT were repeated at Steno Diabetes Center.

Ultrasound scans of the carotid arteries were performed by two technicians, and mean and maximum IMT of the common carotid artery were subsequently analysed using specialised software, and averaged from the left and right side. In addition, atherosclerotic plaques in the left and right bifurcation, and the common and internal carotid artery, were quantified. 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, occasionally, information about which insulin analogue the participant used was given to the technician. A description (see online supplementary appendix 2) of carotid IMT analysis and reproducibility has been reported.<sup>18 19</sup>

### Outcomes

Primary outcome was change in mean carotid IMT of the common carotid arteries. Secondary outcomes were episodes of hypoglycaemia and serious adverse events. Other prespecified explorative outcomes were changes in maximal carotid IMT, number of atherosclerotic plaques, glycaemic control (HbA<sub>1c</sub>, fasting plasma glucose, insulin and C peptide), insulin dose and weight. In the pre-planned data analyses, carotid intima-media area, relative compliance and incremental elastic modulus were included as explorative outcomes. Other prespecified explorative outcomes will be reported separately.<sup>18</sup>

### Statistical analyses

Sample size estimation was based on the primary hypothesis of metformin being superior to placebo with regard to change in carotid IMT. Owing to the 2×3 factorial designs and the choice of five possible group comparisons, the  $\alpha$  value was set to 0.01 for preserving an overall 5% family-wise error. With an estimated 900 participants providing a power of 85% to detect a relevant difference of 0.018 mm in carotid IMT assuming a population SD of 0.075 mm between metformin and placebo during 18 months, comparisons between the three insulin regimens achieves a power of approximately 70% to detect or reject an effect similar to that of statins reported in the meta-analysis by Espeland *et al.*<sup>18 20</sup> Missing data on the primary outcome were imputed using multiple imputation.<sup>21</sup> 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 analysis was adjusted only for baseline value of carotid IMT. Analysis of explorative outcomes was 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.<sup>17</sup> 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 post hoc calculated the significance level adjusted to  $0.05/((K+1)/2)$  (where K represents the number of prespecified secondary outcomes).<sup>22</sup>

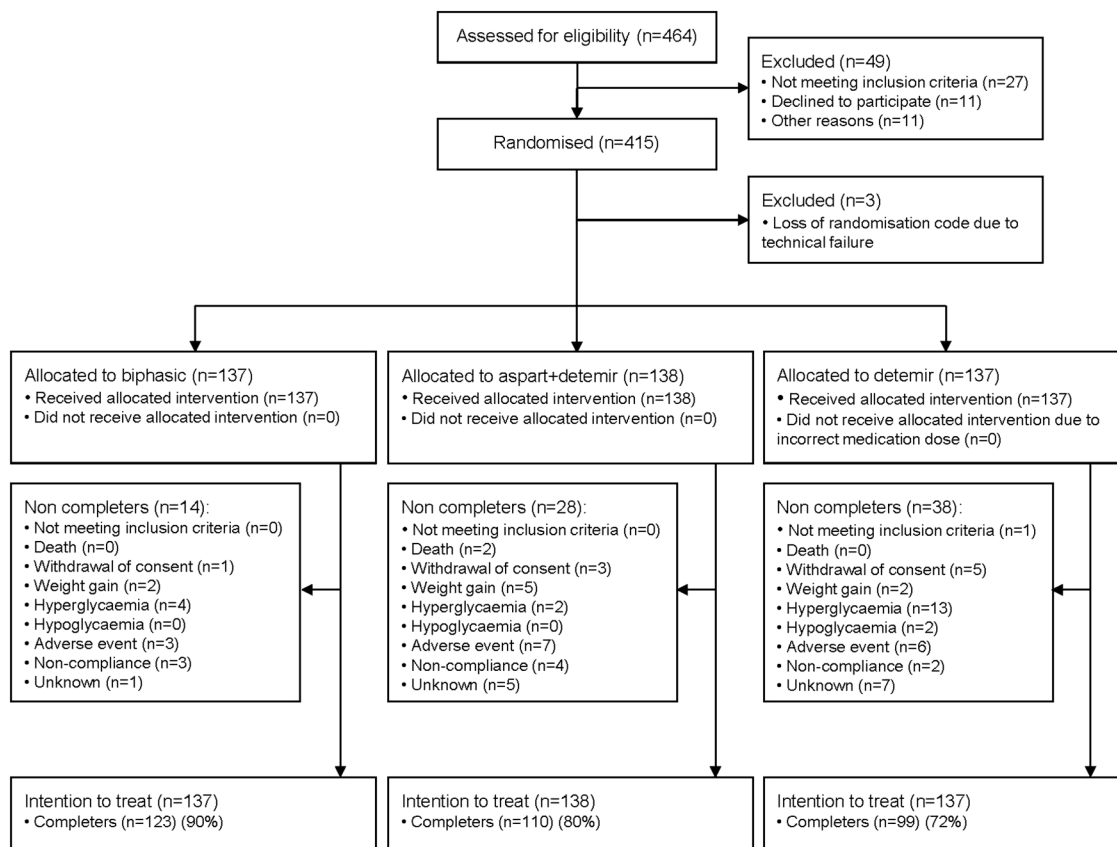
All analyses were made in the statistical program R (R Core Team. R: A language and environment for statistical computing. 16-1-2014. Vienna, Austria: R Foundation for Statistical Computing, 2013).

### RESULTS

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

#### Trial participants and interventions

We assessed 464 participants for eligibility to participate and 415 underwent randomisation. The randomisation code for the blinded metformin/placebo treatment was lost for three participants due to server failure during the trial, and those participants were excluded from the analysis. In addition to intervention with metformin/placebo, 137 participants were randomised to the biphasic group (123 (90%) completers), 138 to the aspart+detemir group (110 (80%) completers) and 137 to the detemir group (99 (72%) completers). The number of completers was significantly higher in the biphasic group compared with the aspart+detemir ( $p=0.024$ ) and detemir ( $p=0.001$ ) groups. More patients in the detemir group dropped out due to hyperglycaemia as compared with the other treatment groups (figure 1). Whenever possible, participants not completing the trial came to a final visit including measurement of carotid IMT (ie, the number of participants not attending the final visit was 10 (7%) in the biphasic group, 11 (8%) in the aspart+detemir group and 17 (12%) in the detemir group). As shown in table 1, the participants were well matched at trial entry (age of 60–61 years, mean duration of T2D of 13 years and ~70% receiving insulin treatment at trial entry). In the biphasic group, injections were increased from one to two daily injections in 65 (47%) participants and to three daily injections in 63 (46%) participants. In the aspart+detemir group, insulin detemir was administered once daily according to the trial design. In the detemir group, the number of injections was increased from one time to two times daily in 110 (80%) participants, and



**Figure 1** Flow of participants through trial.

additional mealtime insulin aspart was prescribed in 32 (23%) participants.

### Change in carotid IMT and other ultrasound-derived variables

Mean carotid IMT changes did not differ between the three groups (biphasic vs aspart+detemir  $p=0.27$ , biphasic vs detemir  $p=0.82$ , aspart+detemir vs detemir  $p=0.19$ , [figure 2](#) and [table 2](#)). The change in mean carotid IMT during the 18 months of intervention in the biphasic group was  $-0.009$  mm (95% CI  $-0.022$  to  $0.004$ ),  $p=0.17$ , in the detemir group  $-0.012$  mm (95% CI  $-0.025$  to  $0.000$ ),  $p=0.06$ , and in the aspart+detemir group  $0.000$  mm (95% CI  $-0.013$  to  $0.013$ ),  $p=0.99$ . Change in maximum carotid IMT did not differ between the insulin groups. No between-group differences were observed in other ultrasound derived variables (data not shown). The interaction between metformin/placebo and insulin regimens did not reach statistical significance ( $p=0.085$ ) as also reported in the detailed account of all statistical analyses at <http://bendixcarstensen.com/SDC/CIMT/DOM/CIMT.pdf>

### Glycaemic control, weight and insulin doses

HbA<sub>1c</sub> was reduced in all three groups ( $p<0.01$ ), but significantly more in the biphasic compared with the aspart+detemir and detemir groups, [table 2](#) and [figure 3](#). HbA<sub>1c</sub> levels at the end of the trial were not optimal, but

lower in the biphasic compared with the aspart+detemir and detemir groups,  $p$  (between groups)  $<0.001$  ([table 2](#)). Fasting plasma glucose levels were reduced in all three groups ([table 2](#) and [figure 3](#)), however, significantly more so in the detemir ( $-2.4$  mmol/L (95% CI  $-3.1$  to  $-1.8$ ) compared with the aspart+detemir group ( $-1.3$  mmol/L ( $-1.9$  to  $-0.7$ ),  $p$  (between groups) =  $0.01$ ). Fasting plasma C peptide and insulin levels decreased in all three groups, but was less reduced in the biphasic compared with the aspart+detemir and detemir groups ([table 2](#)). The variables p-insulin, C peptide, insulin dose, very low-density lipoprotein (VLDL) 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. Weight increased in all three groups; however, the weight gain was significantly more pronounced in the biphasic (3.3 kg (95% CI 2.7 to 4.0)) and aspart+detemir groups (3.2 kg (2.6 to 3.9)) compared with the detemir group (1.9 kg (1.3 to 2.6), [table 2](#) and [figure 3](#)). The prescribed insulin dose increased progressively during the 18 months in all three groups. End-of-trial insulin dose was lowest in the biphasic (0.96 IU/kg/day (95% CI 0.86 to 1.08)) and highest in the detemir (1.58 IU/kg/day (1.40 to 1.78)), whereas the aspart+detemir group was in between (1.15 IU/kg/day (1.02 to 1.29), [table 2](#) and [figure 3](#)). Insulin dose

**Table 1** Baseline characteristics of participants by allocation group

|   | Biphasic (n=137) | Aspart+detemir (n=138) | Detemir (n=137) |
|---|------------------|------------------------|-----------------|
| Age (years)                                   | 61.1 (5.6)       | 60.2 (9.3)             | 60.5 (8.9)      |
| N (%) male                                    | 90 (65.7)        | 96 (69.6)              | 95 (69.3)       |
| Weight (kg)                                   | 95.6 (14.8)      | 97.5 (15.0)            | 98.5 (15.1)     |
| Body mass index*                              | 31.8 (4.4)       | 32.2 (3.9)             | 32.4 (4.3)      |
| Waist-hip ratio                               | 1.00 (0.08)      | 1.00 (0.08)            | 1.01 (0.09)     |
| N (%) smokers                                 | 27 (19.7)        | 19 (13.8)              | 17 (12.6)       |
| Median (IQR) alcohol consumption (units/week) | 2 (0-5)          | 2 (0-5)                | 2 (0-6)         |
| N (%) Caucasians                              | 133 (97.1)       | 133 (96.4)             | 136 (99.3)      |
| <b>Diabetes and complications</b>             |                  |                        |                 |
| Duration of type 2 diabetes (years)           | 12.9 (6.5)       | 12.9 (6.5)             | 12.9 (6.2)      |
| N (%) GAD65 antibodies $\geq 25$ U/mL         | 10 (7.3)         | 9 (6.5)                | 11 (8.0)        |
| HbA <sub>1c</sub> (%)                         | 8.6 (1.0)        | 8.5 (1.0)              | 8.5 (1.1)       |
| HbA <sub>1c</sub> (mmol/mol)                  | 70 (11)          | 69 (11)                | 69 (12)         |
| Fasting p-glucose (mmol/L)                    | 10.7 (3.5)       | 9.9 (3.1)              | 10.4 (3.1)      |
| Median (IQR) fasting p-insulin (pmol/L)       | 68 (38-103)      | 75 (45-132)            | 65 (37-114)     |
| Median (IQR) fasting C peptide (pmol/L)       | 782 (418-1150)   | 828 (507-1217)         | 877 (466-1280)  |
| N (%) prior CVD†                              | 35 (25.6)        | 29 (21.0)              | 36 (26.3)       |
| N (%) microalbuminuria                        | 35 (26.5)        | 23 (17.0)              | 30 (22.2)       |
| N (%) macroalbuminuria                        | 5 (3.8)          | 8 (5.9)                | 7 (5.2)         |
| eCCr‡ (mL/min)                                | 129 (45)         | 130 (45)               | 124 (43)        |
| N (%) simple retinopathy                      | 38 (28.4)        | 42 (31.3)              | 42 (31.3)       |
| N (%) proliferative retinopathy               | 10 (7.5)         | 6 (4.5)                | 9 (6.7)         |
| N (%) prior laser treatment                   | 16 (11.9)        | 7 (5.1)                | 14 (10.5)       |
| N (%) autonomous neuropathy                   | 23 (16.9)        | 22 (16.1)              | 24 (17.7)       |
| N (%) peripheral neuropathy                   | 48 (35.0)        | 46 (33.6)              | 60 (44.1)       |
| <b>Blood pressure and lipids</b>              |                  |                        |                 |
| Systolic blood pressure (mm Hg)               | 138.5 (15.1)     | 139.8 (14.8)           | 139.8 (16.1)    |
| Diastolic blood pressure (mm Hg)              | 82.2 (9.2)       | 82.4 (9.3)             | 81.8 (9.4)      |
| Heart rate (bpm)                              | 77 (13)          | 76 (11)                | 77 (11)         |
| Total cholesterol (mmol/L)                    | 4.1 (0.9)        | 4.2 (1.0)              | 4.1 (1.0)       |
| LDL cholesterol (mmol/L)                      | 2.1 (0.8)        | 2.3 (0.8)              | 2.2 (0.8)       |
| Median (IQR) VLDL cholesterol (mmol/L)        | 0.7 (0.5-1.0)    | 0.7 (0.5-0.9)          | 0.7 (0.5-1.0)   |
| HDL cholesterol (mmol/L)                      | 1.2 (0.4)        | 1.1 (0.3)              | 1.1 (0.3)       |
| Median (IQR) triglycerides (mmol/L)           | 1.5 (1.0-2.3)    | 1.6 (1.2-2.1)          | 1.6 (1.2-2.4)   |
| <b>Medication</b>                             |                  |                        |                 |
| N (%) metformin§                              | 111 (81.0)       | 114 (82.6)             | 118 (86.8)      |
| N (%) insulin§                                | 94 (68.6)        | 96 (69.6)              | 95 (69.3)       |
| N (%) sulfonylurea§                           | 39 (28.5)        | 40 (29.0)              | 37 (27.2)       |
| N (%) other antihyperglycaemic drug§          | 17 (12.4)        | 17 (12.3)              | 25 (18.3)       |
| N (%) RAS blockade                            | 106 (77.4)       | 102 (73.9)             | 100 (73.0)      |
| N (%) other antihypertensive drug             | 79 (57.7)        | 73 (52.9)              | 81 (59.1)       |
| N (%) statin                                  | 116 (84.7)       | 116 (84.1)             | 119 (86.9)      |
| N (%) aspirin                                 | 80 (58.4)        | 79 (57.3)              | 72 (52.6)       |
| <b>Carotid ultrasound measures</b>            |                  |                        |                 |
| Mean carotid IMT (mm)                         | 0.786 (0.121)    | 0.796 (0.148)          | 0.798 (0.139)   |
| Maximal carotid IMT (mm)                      | 0.949 (0.140)    | 0.954 (0.165)          | 0.965 (0.155)   |
| Relative compliance $\times 10^3$ (mm/Hg)     | 2.5 (1.0)        | 2.6 (1.1)              | 2.6 (1.1)       |
| Incremental elastic modulus (mm Hg)           | 2377 (1073)      | 2314 (1012)            | 2348 (1009)     |
| Carotid intima-media area (mm <sup>2</sup> )  | 18.64 (4.10)     | 19.28 (5.14)           | 19.49 (4.89)    |
| Median (IQR) number of plaques¶               | 3 (2-4)          | 2 (1-4)                | 3 (2-5)         |

Values are means (SDs) unless stated otherwise.

\*Body mass index is calculated as weight (kg) divided by height (m)<sup>2</sup>.

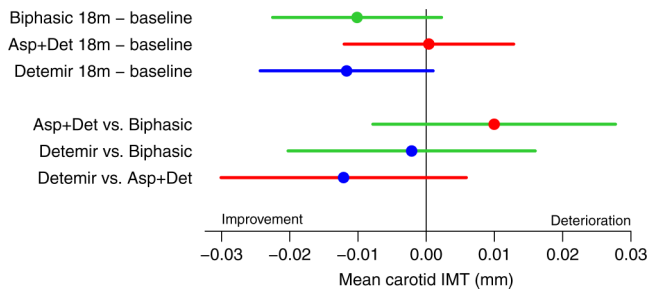
†Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, vascular surgery, stroke, transitory cerebral ischaemia and amputation.

‡Calculated by the Cockcroft-Gault equation: eCCr=(140-age) $\times$ weight (kg) $\times$ constant/serum creatinine ( $\mu$ mol/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<sub>1c</sub>, glycated haemoglobin; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; RAS, renin angiotensin system; VLDL, very low-density lipoprotein.



**Figure 2** Changes from baseline and differences between treatments in mean carotid intima-media thickness (IMT) (mean (95% CI)) during 18 months treatment with three insulin regimens: biphasic (green), aspart (Asp)+detemir (Det) (red) and detemir (blue), from the random-effects model with baseline as covariate using multiply imputed data, adjusted for stratification variables.

represents the dose prescribed by the investigator at each visit for the following 3 months, hence the last insulin dose registered is at 15 months (figure 3), being the last dose prescribed for the last 3 months in the trial.

### Hypoglycaemia and serious adverse events

No differences were found in the number of participants with at least one episode of severe hypoglycaemia (table 3). The total number of severe hypoglycaemic episodes was 4 in the biphasic compared with 16 episodes in the aspart+detemir group ( $p=0.01$ ) and 7 episodes in the detemir group ( $p=0.38$ ). The total number of non-severe hypoglycaemic episodes during 18 months differed between all three groups ( $p<0.001$ ), with most episodes in the biphasic (2823) and fewest episodes in the detemir (2115) group (table 3). No differences were found with regard to serious adverse events (table 3 and see online supplementary tables S1 and S2). Numbers of adverse events are shown in online supplementary tables S3 and S4.

### Blood pressure and lipids

Blood pressure was significantly reduced in all three groups during the trial, without any between-group differences (table 2). Low-density lipoprotein cholesterol level increased by 0.15 mmol/L (95% CI 0.04 to 0.27),  $p=0.010$  in the biphasic and 0.17 (95% CI 0.05 to 0.29),  $p=0.007$  in the detemir group, without significant between-group differences (table 2). Triglyceride as well as high-density lipoprotein and VLDL cholesterol levels did not change significantly in any of the three groups (table 2).

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

## DISCUSSION

In this randomised clinical trial, we observed no significant differences in the change of mean carotid IMT in

participants with T2D during 18 months of treatment between the three insulin analogue regimens with or without adjunct metformin treatment. All three insulin regimens reduced HbA<sub>1c</sub> level, however, the reduction of HbA<sub>1c</sub> was significantly more pronounced with biphasic insulin aspart despite lower doses of insulin. Weight gain was greater in the biphasic and in the aspart+detemir group compared with the insulin detemir only group. The highest number of non-severe hypoglycaemic episodes was reported from the biphasic group, whereas severe hypoglycaemic episodes occurred most often in the aspart+detemir group.

Randomised trials evaluating the effect of different insulin regimens on carotid IMT are sparse. Bibra *et al*<sup>23</sup> reported that 24 months treatment with human regular insulin before main meals was associated with reduced postmeal plasma glucose excursion and lower carotid IMT compared with conventional therapy using pre-mixed insulin in patients with T2D. The ORIGIN-Graace study evaluated insulin glargine titrated to a fasting plasma glucose target of 5.3 mmol/L versus standard glycaemic care in 1184 patients with impaired fasting glucose or early T2D, and reported a significant improvement in maximum carotid IMT of the common carotid artery in the glargine group compared with standard care after a median follow-up of 4.9 years.<sup>24</sup> However, the risk of clinical cardiovascular disease did not differ between the groups in the ORIGIN trial after a median follow-up of 6.2 years.<sup>25</sup> Postprandial hyperglycaemia in patients with T2D has been speculated to be harmful with respect to development and progression of atherosclerosis,<sup>5 26 27</sup> and treatments targeting postprandial glucose excursion have been suggested to be associated with significantly improved carotid IMT.<sup>28 29</sup> In order to test this, we compared patients treated with the basal-bolus insulin regimen with patients treated with basal insulin only. Furthermore, we included the more pragmatic treatment option to reduce postprandial hyperglycaemia with a premixed combination of 30% rapid-acting and 70% intermediate-acting insulin aspart administered between one and three times daily, as required. Our results, however, do not support a beneficial cardiovascular effect of targeting postprandial hyperglycaemia.

Despite higher glycaemic levels and insulin doses, participants randomised to basal insulin detemir were the only group showing a non-significant improvement in carotid IMT during the intervention period ( $p=0.06$ ). The extent to which intensified glycaemic control reflected by a reduction in HbA<sub>1c</sub> level is associated with a reduced cardiovascular risk in T2D remains controversial.<sup>30</sup> In the HEART2D trial, survivors of acute myocardial infarction were randomised to treatment with prandial versus basal insulin, and no difference in risk for future cardiovascular events was reported.<sup>31</sup> We found inferior glycaemic control in patients randomised to insulin detemir with or without combination with insulin aspart compared with premixed insulin aspart,

**Table 2** Changes in outcome from trial entry to 18 months\*

|   | Biphasic (n=137)         | Aspart+detemir (n=138)  | Detemir (n=137)           | p Value biphasic vs aspart+detemir | p Value biphasic vs detemir | p Value aspart +detemir vs detemir |
|---|--------------------------|-------------------------|---------------------------|------------------------------------|-----------------------------|------------------------------------|
| <b>Carotid ultrasound measures</b>                              |                          |                         |                           |                                    |                             |                                    |
| Mean carotid IMT (mm)†  | -0.009 (-0.022 to 0.004) | 0.000 (-0.013 to 0.013) | -0.012 (-0.025 to 0.000)  | 0.2720                             | 0.8173                      | 0.1871                             |
| Maximal carotid IMT (mm)  | -0.010 (-0.025 to 0.005) | 0.001 (-0.014 to 0.016) | -0.016 (-0.031 to -0.001) | 0.2935                             | 0.5734                      | 0.1095                             |
| <b>Body composition</b>   |                          |                         |                           |                                    |                             |                                    |
| Weight (kg)   | 3.3 (2.7 to 4.0)         | 3.2 (2.6 to 3.9)        | 1.9 (1.3 to 2.6)          | 0.8102                             | 0.0026                      | 0.0055                             |
| Body mass index (kg/m <sup>2</sup> )                            | 1.1 (0.9 to 1.3)         | 1.0 (0.8 to 1.2)        | 0.6 (0.4 to 0.8)          | 0.7037                             | 0.0021                      | 0.0071                             |
| Waist-hip ratio   | 0.00 (-0.01 to 0.01)     | 0.01 (0.00 to 0.02)     | 0.01 (0.00 to 0.02)       | 0.0926                             | 0.0484                      | 0.7516                             |
| <b>Glycaemic control</b>  |                          |                         |                           |                                    |                             |                                    |
| HbA <sub>1c</sub> (%)   | -1.00 (-1.16 to -0.83)   | -0.45 (-0.61 to -0.28)  | -0.26 (-0.43 to -0.09)    | <0.001                             | <0.001                      | 0.1304                             |
| HbA <sub>1c</sub> (mmol/mol)                                    | -10.9 (-12.7 to -9.1)    | -4.9 (-6.7 to -3.1)     | -2.8 (-4.7 to -1.0)       | <0.001                             | <0.001                      | 0.1304                             |
| HbA <sub>1c</sub> at 18 months (%)                              | 7.78 (7.56 to 8.00)      | 8.19 (7.98 to 8.42)     | 8.42 (8.20 to 8.64)       | 0.0019                             | <0.001                      | 0.1074                             |
| HbA <sub>1c</sub> at 18 months (mmol/mol)                       | 62 (59 to 64)            | 66 (64 to 69)           | 69 (66 to 71)             | 0.0019                             | <0.001                      | 0.1074                             |
| N (%) participants with HbA <sub>1c</sub> ≤7.0% at end-of-trial | 38 (28)                  | 31 (22)                 | 12 (9)                    | 0.306                              | 0.000                       | 0.005                              |
| Fasting p-glucose, mmol/L                                       | -2.0 (-2.6 to -1.4)      | -1.3 (-1.9 to -0.7)     | -2.4 (-3.1 to -1.8)       | 0.1108                             | 0.3347                      | 0.0109                             |
| Fasting p-insulin (relative change from baseline)               | 0.92 (0.78 to 1.09)      | 0.57 (0.48 to 0.67)     | 0.52 (0.44 to 0.62)       | <0.001                             | <0.001                      | 0.5103                             |
| Fasting C peptide (relative change from baseline)               | 0.85 (0.76 to 0.94)      | 0.70 (0.63 to 0.78)     | 0.60 (0.54 to 0.67)       | 0.0110                             | <0.001                      | 0.0480                             |
| Insulin dose, end-of-trial (IU/kg/day)                          | 0.96 (0.86 to 1.08)      | 1.15 (1.02 to 1.29)     | 1.58 (1.40 to 1.78)       | 0.0064                             | <0.001                      | <0.001                             |
| Insulin dose, end-of-trial (IU/day)                             | 95 (84 to 108)           | 116 (102 to 132)        | 158 (139 to 180)          | 0.080                              | <0.001                      | <0.001                             |
| Insulin dose (relative change from baseline)                    | 1.96 (1.82 to 2.11)      | 2.27 (2.10 to 2.45)     | 3.37 (3.11 to 3.65)       | 0.006                              | <0.001                      | <0.001                             |
| <b>Blood pressure and lipids</b>                                |                          |                         |                           |                                    |                             |                                    |
| Systolic blood pressure (mm Hg)                                 | -6.7 (-9.4 to -3.9)      | -6.0 (-8.8 to -3.1)     | -3.5 (-6.4 to -0.6)       | 0.7282                             | 0.1249                      | 0.2391                             |
| Diastolic blood pressure (mm Hg)                                | -3.3 (-4.8 to -1.8)      | -2.9 (-4.4 to -1.4)     | -3.5 (-5.1 to -1.9)       | 0.6996                             | 0.8795                      | 0.5998                             |
| Heart rate (bpm)  | -1.3 (-3.1 to 0.4)       | -0.5 (-2.3 to 1.2)      | -3.0 (-4.8 to -1.2)       | 0.5168                             | 0.1853                      | 0.0532                             |
| Total cholesterol (mmol/L)                                      | 0.17 (0.03 to 0.31)      | 0.05 (-0.09 to 0.19)    | 0.19 (0.05 to 0.33)       | 0.2323                             | 0.8254                      | 0.1603                             |
| LDL cholesterol (mmol/L)  | 0.15 (0.04 to 0.27)      | 0.06 (-0.06 to 0.18)    | 0.17 (0.05 to 0.29)       | 0.2634                             | 0.9012                      | 0.2187                             |
| VLDL cholesterol (relative change from baseline)                | 0.96 (0.90 to 1.03)      | 1.02 (0.95 to 1.09)     | 1.01 (0.94 to 1.09)       | 0.2821                             | 0.3111                      | 0.9578                             |
| HDL cholesterol (mmol/L)  | 0.03 (-0.00 to 0.07)     | -0.01 (-0.05 to 0.03)   | -0.01 (-0.05 to 0.02)     | 0.1112                             | 0.0840                      | 0.8722                             |
| Triglycerides (relative change from baseline)                   | 0.97 (0.91 to 1.05)      | 1.00 (0.93 to 1.08)     | 1.02 (0.95 to 1.10)       | 0.5826                             | 0.3541                      | 0.6989                             |

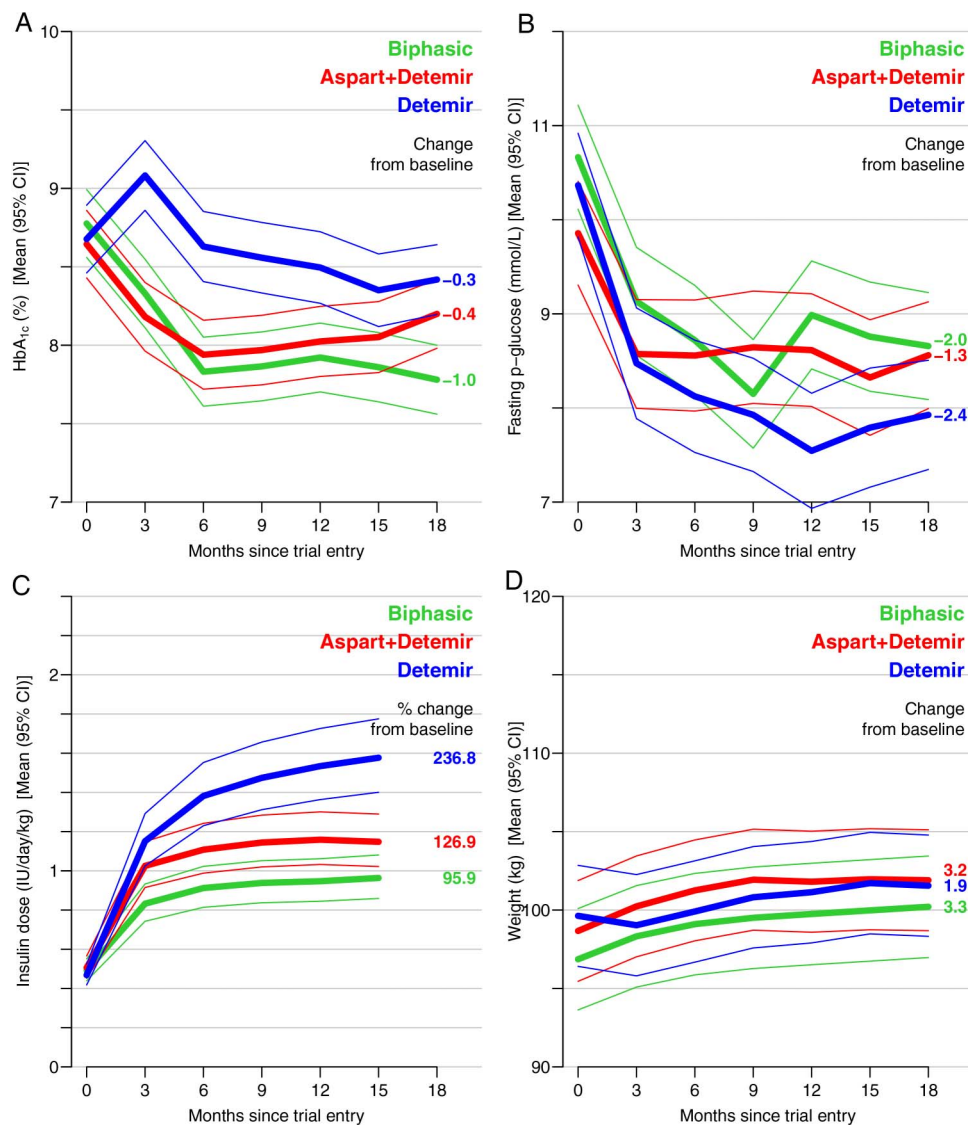
The variables p-insulin, C peptide, insulin dose, VLDL cholesterol and triglycerides did not meet the criteria of a normal distribution and were accordingly log transformed. Therefore, these variables are presented in table 2 with relative change from baseline instead of absolute change.

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  $\alpha=0.0045$ .

\*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.

HbA<sub>1c</sub>, glycated haemoglobin; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.



**Figure 3** Changes (mean (95% CI)) during 18 months treatment with three insulin regimens: biphasic (green), aspart-detemir (red) and detemir (blue) in glycated haemoglobin ( $HbA_{1c}$ ) (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.

but no significant differences between treatments in carotid IMT after 18 months. The fact that 23% of the patients in the detemir group needed an additional insulin aspart injection reflects the increasing recognition during the trial that insulin detemir was an ineffective way to control blood glucose in T2D patients with long mean duration of about 13 years. Theoretically, this could to some extent have masked a beneficial effect of meal rapid-acting insulin administration on outcomes including carotid IMT. However, given the much more widespread use of meal rapid acting insulin in patients on multiple injections, we find it highly unlikely to have influenced our results. Accordingly, the results from randomised clinical trials do not, in contrast to some epidemiological studies, support a simple relation between glycaemic levels and risk of clinical cardiovascular disease. Hyperinsulinaemia has been proposed as an

isolated risk factor for atherosclerosis in people with and without diabetes.<sup>32–33</sup> Experimental studies have provided some support for this hypothesis.<sup>34–36</sup> However, despite quantitatively major differences in total insulin doses with the highest doses in the detemir-based regimens, no significant differences in progression rates of carotid IMT were detected. In accordance, the UK Prospective Diabetes Study (UKPDS) did not support hyperinsulinaemia as being a risk factor of cardiovascular disease in patients with T2D.<sup>37</sup> Lastly, increased BMI is a risk factor of cardiovascular disease.<sup>38</sup> Whether the less weight gain in the detemir group to some extent may be reflected in the trend towards a more beneficial effect on carotid IMT changes in this group cannot be revealed from the present data. The Treating To Target in Type 2 diabetes (4-T) trial compared the metabolic effects of three insulin treatment modalities in patients



**Table 3** Hypoglycaemia and serious adverse events during 18 months according to insulin regimens

|  | Biphasic<br>(n=137) | Aspart<br>+detemir<br>(n=138) | Detemir<br>(n=137) | p Value                           |                        |                                  |
|--|---------------------|-------------------------------|--------------------|-----------------------------------|------------------------|----------------------------------|
|  |                     |                               |                    | Biphasic<br>vs aspart<br>+detemir | Biphasic vs<br>detemir | Aspart<br>+detemir vs<br>detemir |
| Severe hypoglycaemia (number of patients with at least 1 event, N (%))   | 3 (2.2)             | 5 (3.6)                       | 6 (4.4)            | 0.4859                            | 0.3205                 | 0.7500                           |
| Severe hypoglycaemia (number of events (rate among patients with at least 1 event))                                  | 4 (1.3)             | 16 (3.2)                      | 7 (1.2)            | 0.0141                            | 0.3770                 | 0.0707                           |
| Non-severe hypoglycaemia (number of patients with at least one event, N (%))   | 110 (80.3)          | 108 (78.2)                    | 95 (69.3)          | 0.6778                            | 0.0375                 | 0.0927                           |
| Non-severe hypoglycaemia (number of events (rate among patients with at least 1 event))                              | 2823 (25.7)         | 2570 (23.8)                   | 2115 (22.3)        | <0.001                            | <0.001                 | <0.001                           |
| Serious adverse events excluding severe hypoglycaemia (number of patients with at least 1 event, N (%))              | 37 (27.0)           | 31 (22.5)                     | 31 (22.6)          | 0.3826                            | 0.4072                 | 0.9658                           |
| Serious adverse events excluding severe hypoglycaemia (number of events (rate among patients with at least 1 event)) | 64 (1.7)            | 45 (1.5)                      | 44 (1.4)           | 0.0656                            | 0.0588                 | 0.9555                           |

Severe hypoglycaemia is 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 plasma glucose  $\leq 3.9$  mmol/L.

with T2D during 3 years.<sup>6 39</sup> The initial treatment arms included basal insulin detemir, premixed insulin aspart as well as insulin aspart administered before meals. Our finding of improved HbA<sub>1c</sub> among patients treated with premixed insulin aspart compared with insulin detemir only is consistent with the 1-year outcome data of the 4-T trial, although the absolute differences in HbA<sub>1c</sub> in our trial were markedly higher.<sup>6 39</sup> This may be explained by differences in participant characteristics, with those in the 4-T trial being insulin naïve prior to the trial and treated with insulin in combination with metformin and sulfonylurea.

### Strengths and limitations

The strength of the CIMT trial is the randomised design and the fact that all ultrasound scans were centrally performed by only two technicians, with good reproducibility.<sup>19 40 41</sup> A limitation is the use of carotid IMT instead of clinical events as primary outcome, as previously discussed.<sup>17</sup> In terms of sample size, a rather conservative approach was applied due to the plan of multiple comparisons between intervention groups testing the effect of adjunct metformin treatment versus placebo and the three insulin regimens simultaneously. We therefore used an  $\alpha$  of 0.01 and obtained a power of 70% of the insulin comparisons, while a conventional approach using an  $\alpha$  of 0.05 might have increased the overall family-wise type 1 error rate for the five planned comparisons to 0.25.<sup>18</sup> Owing to slow 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 patients with T2D, we were only able to include approximately half of the participants originally planned for in this trial.<sup>17</sup> However, the total number of participants in the current trial was twofold higher than the total number of participants included in a trial of repaglinide versus glyburide reporting an effect of 12 months treatment with repaglinide on carotid IMT.<sup>28</sup> Our sample size estimation was also conservative compared with the Carotid Atherosclerosis: METformin for insulin ResistAnce (CAMERA) trial evaluating the effect of 18 months treatment with metformin versus placebo in 173 patients without diabetes with established cardiovascular disease, also using carotid IMT as the primary outcome.<sup>42</sup> In the CAMERA trial, a sample size of 180 participants was estimated, compared with our 900, illustrating the difficulties in performing sample size estimation when reliable data are not available. Another limitation was failure to reach good glycaemic control. Despite provision of a detailed guideline with a treat-to-target approach, obtaining adequate glycaemic control proved difficult in many patients. Especially, insulin detemir administered once daily was not sufficient to lower glucose levels in the majority of participants, although insulin doses were titrated aggressively.

### CONCLUSION

In conclusion, despite differences in HbA<sub>1c</sub> levels, weight gain and insulin doses, we did not find any significant differences in the progression rates of carotid IMT when treating patients with long-term T2D with

three different frequently used insulin analogues regimens targeting postprandial and/or fasting plasma glucose. Further research is warranted addressing the question to what extent different insulin analogue regimens targeting basal and/or postprandial hyperglycaemia may influence the risk of cardiovascular disease in a differential manner.

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