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Study rationale and design of the CIMT trial: The Copenhagen Insulin and Metformin Therapy Trial

L. Lundby Christensen,[1] T. Almdal,[2] T. Boesgaard,[1] L. Breum,[3] E. Dunn,[4] B. Gade-Rasmussen,[5] C. Gluud,[6] C. Hedetoft,[3] A. Jarloev,[5] T. Jensen,[7] T. Krarup,[8] L. B. Johansen,[9] S. S. Lund,[1] S. Madsbad,[2] E. Mathiesen,[7] J. Moelvig,[9] F. Nielsen,[10] H. Perrild,[8] O. Pedersen,[1] M. Roeder,[11] S. B. Sneppen,[4] O. Snorgaard,[2] L. Tarnow,[1] B. Thorsteinsson,[11] A. Vaag,[1] H. Vestergaard,[10] J. Wetterslev[6] and N. Wiinberg[12], The CIMT Trial Group

[1]Steno Diabetes Center, Gentofte, Denmark
[2]Department of Endocrinology, Hvidovre University Hospital, Hvidovre, Denmark
[3]Department of Medicine, Koege Sygehus, Koege, Denmark
[4]Department of Medicine F, Gentofte Hospital, Gentofte, Denmark
[5]Department of Medicine, Frederiksberg Hospital, Frederiksberg, Denmark
[6]Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark
[7]Department of Endocrinology PE, Rigshospitalet, Copenhagen, Denmark
[8]Department of Medicine I, Bispebjerg Hospital, Copenhagen, Denmark
[9]Department of Medicine, Amager Hospital, Copenhagen, Denmark
[10]Department of Endocrinology J, Herlev Hospital, Herlev, Denmark
[11]Department of Endocrinology, Hilleroed Hospital, Hilleroed, Denmark
[12]Department of Nuclear Medicine, Frederiksberg Hospital, Frederiksberg, Denmark

Background: Patients with type 2 diabetes (T2DM) have an increased mortality rate primarily because of macrovascular disease. Where T2DM patients cannot be managed sufficiently through diet, exercise and peroral antidiabetic drugs, that is when haemoglobin A1c (HbA1c) is above 7.0%, it is yet unknown whether a combination of metformin and insulin analogues is superior to insulin analogues alone. Nor is it known which insulin analogue regimen is the optimal.

Objective: The primary objective of this trial is to evaluate the effect of an 18-month treatment with metformin vs. placebo in combination with one of three insulin analogue regimens, the primary outcome measure being carotid intima-media thickness (CIMT) in T2DM patients.

Design: A randomized, stratified, multicentre trial having a 2×3 factorial design. The metformin part is double masked and placebo controlled. The insulin treatment is open. The intervention period is 18 months.

Patient Population: Nine hundred and fifty patients with T2DM and HbA1c $\geq 7.5\%$ on treatment with oral hypoglycaemic agents or on insulin treatment and deemed able, by the investigator, to manage once-daily insulin therapy with a long-acting insulin analogue.

Randomization: Central randomization stratified for age (above 65 years), previous insulin treatment and treatment centre.

Interventions: Metformin 1 g $\times$ two times daily vs. placebo (approximately 475 patients vs. 475 patients) in combination with

Correspondence:
Louise Lundby Christensen, Department 810, Steno Diabetes Center, Niels Steensens vej 2, 2820 Gentofte, Denmark.
E-mail:
llch@steno.dk

- Insulin detemir before bedtime (approximately 315 patients) or
- Biphasic insulin aspart 30 before dinner with the possibility to increase to two or three injections daily (approximately 315 patients) or
- Insulin aspart before the main meals (three times daily) and insulin detemir before bedtime (approximately 315 patients).

Intervention follows a treat-to-target principle in all six arms aiming for an HbA1c $\leq$ 7.0%.

Outcome Measures: Primary outcome measure is the change in CIMT from baseline to 18 months. Secondary outcome measures comprises the composite outcome of death, acute myocardial infarction, stroke or amputation assessed by an adjudication committee blinded to intervention, other cardiovascular clinical outcomes, average postprandial glucose increment from 0 to 18 months, hypoglycaemia and any inadvertent medical episodes. In addition, change in plaque formation in the carotids, HbA1c, cardiovascular biomarkers, body composition, progression of microvascular complications and quality of life will be assessed as tertiary outcome measures.

Time Schedule: Patient enrolment started May 2008. Follow-up is expected to finish in March 2011.

Conclusion: CIMT is designed to provide evidence as to whether metformin is advantageous even during insulin treatment and to provide evidence regarding which insulin analogue regimen is most advantageous with regard to cardiovascular disease.

Keywords: cardiovascular disease, insulin, intima-media thickness, metformin, type 2 diabetes

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Introduction

Treating patients with type 2 diabetes (T2DM) in its earliest stage can be performed by lifestyle interventions promoting increased activity and weight loss, a minor weight loss of between 2 and 5 kg usually being sufficient at this point to achieve good glycaemic control [1]. Due to the limited long-term success of lifestyle programmes to maintain glycaemic goals in patients with T2DM and given the decreasing insulin secretion during disease progression, it is necessary to initiate peroral antidiabetic therapy, the first choice often being metformin. At later stages, combination therapy with an insulin secretagogue or a glitazone drug can be initiated. At the late stages, a substantial number of patients will necessitate initiation of insulin treatment to achieve therapeutic goals.

As the achievement of these therapeutic goals is typically associated with increased risk of hypoglycaemia and weight gain, treatment regimens have been developed to minimize these two risks. Neutral protamine Hagedorn (NPH) insulin before bedtime in combination with metformin 1 g $\times$ two times daily is often preferred as the initial insulin treatment regimen. This regimen does seem to demonstrate short-term beneficial effects in regard to simplicity, weight increase and hypoglycemic risk [2]. Other health care providers prefer initiating insulin by starting with a premixed insulin preparation before breakfast, possibly supplemented by a second injection before dinner, alone or in combination with metformin [3]. During recent years, regimens combining insulin detemir or insulin glargine with metformin before bed have been introduced. Using insulin detemir or glargine does not in itself ameliorate glycaemic control by lowering haemoglobin A1c (HbA1c) levels; however, several studies have demonstrated a certain reduction in the number of, especially nightly, hypoglycemic episodes as well as a long-term lowering of fasting blood glucose levels [4,5]. Insulin detemir is a long-acting insulin drug, and apart from reducing hypoglycaemia through less day-to-day variation in absorption, it is also associated with less weight gain than human insulin and other insulin analogues in T2DM patients [4].

Only a small number of T2DM patients are treated with multiple injections of rapid-acting insulin before main meals and NPH insulin before bedtime, the reason probably being that this regimen is regarded as relatively unpractical in the case of elderly T2DM patients. Besides, HbA1c levels close to the non-diabetic range is often achieved with fewer insulin injections a day when combined with peroral antidiabetic medication. New studies seem to demonstrate, however, that reduction of postprandial hyperglycaemia in T2DM patients can be decisive for reducing the doubled risk of development and progression of atherosclerosis in T2DM patients, for example through reduction of oxidative stress [6].

T2DM patients are at twofold to fourfold higher risk for cardiovascular disease (CVD) than persons without diabetes [7,8].

It is generally accepted that intensive glycaemic control using insulin therapy reduces the risk of development and progression of microvascular complications in diabetic patients [9,10]. Regarding macrovascular complications, that is CVD, the picture is more

complicated. In the UK Prospective Diabetes Study (UKPDS), it was shown that treatment with metformin reduced the risk of CVD compared with sulfonylureas [11,12]. In June 2008, two large trials, Advance [13], and Accord [14] were reported. These two trials both treated patients with a diabetes duration of 8–10 years, and 30–40% of the patients had established CVD, whereas the patients included in the UKPDS were newly diagnosed in general without clinically known CVD. In the two recent trials, very intensive glucose-lowering treatment regimens were used, resulting in HbA1c of 6.0–6.5% in the intensive arms compared with 7.5–8.5% in the non-intensive arms. A high proportion of the patients in the intensive treatment arms of the two trials received insulin. In the UKPDS [9], HbA1c was 7.4% in the intensive arm compared with 8.0% in the conventional arm. With regard to CVD, no effect of intensive lowering of glucose was found. The significance of these results is not yet clear; however, with regard to glucose lowering, it is, as of June 2008, recommended that the target for HbA1c at least in patients with longer disease duration and CVD should be 7.0% [15]. In the two recent trials, more than 80% of the patients were on metformin, and thus, it is not possible to study whether metformin in itself is advantageous. Therefore, it remains unknown whether the potential cardioprotective effects of metformin observed in the UKPDS are maintained when used in combination with insulin. Moreover, it is still unknown whether progression of macrovascular disease in T2DM patients is differently affected by different insulin regimens; especially, is it not known whether optimized postprandial glucose level management affects on progression of macrovascular disease. In conclusion, it has not been shown, in interventional trials, whether continuing metformin when initiating insulin treatment in T2DM reduces progression of atherosclerosis or whether the type insulin regimen used reduces progression of atherosclerosis and thereby decreases the risk of CVD.

An ideal trial would be one of such scope and power as to enable evaluation of treatment in relation to clinical macrovascular 'hard' end-points, for example acute myocardial infarction (AMI), stroke and amputations. However, such a trial would require a test population of several thousand patients and a minimum trial period of 3–5 years. Carrying out a trial of such dimensions would require substantial funding.

A realistic alternative is to use a potential surrogate marker for measuring the progression of macrovascular disease [16]. The measuring of carotid intima-media thickness (CIMT) complies with the generally accepted requirements for a surrogate end-point: (i) documented epidemiological relation between the surrogate outcome and development of the disease for which it is a marker; (ii) studies showing that the use of a drug results in a significant modification of the marker in a direction associated with significant risk reduction of the clinical outcome; and (iii) demonstrated significant association between the drug-induced decrease in the marker and the clinical outcome.

A relation between changes in CIMT and macrovascular disease has been found in T2DM patients [17–21]. An observational study has shown a correlation between treatment with metformin and gliclazide and reduced risk of macrovascular disease [22].

Prospective studies have been performed using measurement of CIMT as surrogate marker for the effect of treatment with insulin secretagogues and glitazones. A 12-month study demonstrated that repaglinide, in contrast to gliclazide, was associated with CIMT regression [23]. The HbA1c level was found to be identical in both groups and taken to prove that better management of postprandial blood glucose, as seen in repaglinide treatment, is associated with reduced risk of macrovascular disease [23]. Regarding the effect of glitazone treatment, two trials, having a duration of 6 [24] and 18 months [25], respectively, were performed comparing pioglitazone with glimepiride. In both trials, pioglitazone treatment was associated with a significantly lesser development in CIMT. The results of pioglitazone treatment correspond to the results of the PROactive trial, which seemed to indicate that pioglitazone treatment is associated with reduced risk of macrovascular disease [26].

Altogether, it can be concluded

- that it remains uncertain whether metformin in combination with insulin affects CIMT;
- that it remains uncertain whether metformin treatment in combination with insulin is associated with reduced risk of developing macrovascular disease;
- that a change in CIMT is a likely surrogate outcome for the development of macrovascular disease in T2DM patients;
- that optimized treatment of the postprandial blood glucose level seems to have some importance for reducing the risk of developing macrovascular disease. This final point does, however, require further investigation.
- It remains unknown, if any specific insulin treatment regimen provides beneficial effects on CVD outcome compared with other insulin regimens.

The CIMT trial is a 2 × 3 factorial randomized trial designed to provide evidence as to whether metformin is advantageous even during insulin treatment and to provide evidence regarding which insulin regimen is most advantageous with regard to CVD.

Objectives

The primary objective of the CIMT trial is to evaluate the effect of an 18-month treatment with metformin vs. placebo in combination with one of three insulin analogue regimens, the primary outcome measure being CIMT in T2DM patients. The secondary objectives are comparisons of the effect of the three insulin regimens.

The primary explorative objective is to determine whether there is an association between change in postprandial blood glucose exposure and CIMT change.

Patients and Methods

Patients

It is planned to screen approximately 2000 T2DM patients to randomize 950 patients. The patients are recruited from 10 clinical centres in the greater Copenhagen area.

Males and females over 30 years of age are eligible for the trial if they meet the following criteria:

- T2DM (World Health Organization criteria)
- Body mass index: 25–40 kg/m^2 (both limits included)
- HbA1c $\geq$ 7.5%
- Antidiabetic tablet treatment during 1 year minimum and/or
- Insulin treatment during a minimum period of 3 months, where investigator deems the patient capable of insulin therapy × once daily
- Negative pregnancy test
- Signed informed consent

All patients will provide written informed consent before participation. The protocol has been approved by the regional ethical committee (region of Copenhagen journal number H-D-2007-112) and the Danish Medicines Agency (journal number 2612-3648), reported to the Danish Data Protection Agency, registered with ClinicalTrials.gov (NCT00657943)) and will be conducted in accordance with The Helsinki Declaration and guidelines for Good Clinical Practice.

Trial interventions

In patients previously treated with sulphonylurea, insulin or other antidiabetic medications these interventions will be stopped. Patients are randomly assigned in a 2 × 3 factorial design to metformin or placebo as well as to one of three insulin analogue regimens.

The metformin treatment is double blinded and placebo controlled. Irrespective of previous metformin treatment and dose, a maintenance dose of 1000 mg twice daily will be given. In case of any suspected adverse effects, the investigator may decide to reduce medication temporarily by, for example, 500 mg.

Patients are randomly assigned to one of the following insulin regimens:

- Insulin detemir once daily before bedtime.
- Biphasic insulin aspart 30 before dinner with possible increase to two or three daily injections.
- Insulin aspart before the main meals (three times daily) and detemir before bedtime.

Insulin therapy is open and based on insulin analogues (figure 1).

The insulin regimen is a treat-to-target trial with a goal of HbA1c of 7.0% giving due consideration to the risk of hypoglycaemia in the individual patient. Insulin dose will be adjusted according to predefined algorithms.

Fig. 1 Trial outline.

Adjustment of insulin dose during the first 12 weeks will be carried out by at least weekly telephonic contact with a diabetic nurse. After the 12th week, telephone contacts will be every 2 or 3 weeks.

Antihypertensives

Therapeutic goals for blood pressure during the trial are the following:

- For patients without microalbuminuria (urinary albumin excretion: <30 mg/day, <20 μmol/min, <30 mmol/g creatinine): systolic blood pressure ≤130 mmHg and diastolic blood pressure ≤80 mmHg.
- For patients with increased urinary albumin excretion (urinary albumin excretion: ≥30 mg/day, ≥20 μmol/min, ≥30 mmol/g creatinine): systolic blood pressure ≤125 mmHg and diastolic blood pressure ≤80 mmHg.

If blood pressure, systolic or diastolic, exceeds these therapeutic goals, the patient will be medically treated with one or several drugs, basic treatment consisting generally of angiotensin converting enzyme (ACE) inhibitor or angiotensin 2 receptor blocker at investigators discretion.

Lipid Lowering

Therapeutic goals for lipids during the trial are the following:

- Total cholesterol below 4.5 mmol/l and
- LDL cholesterol below 2.5 mmol/l.

Basic medical treatment consisting of statins at investigators discretion. If goals are not reached, other lipid-lowering drugs should be added at the discretion of the investigator.

Antiplatelet Therapy

All patients are treated with acetylsalicylic acid at a minimum dose of 75 mg per 24 h, unless in case of a contraindication.

Randomization

A central, computer-based randomization service will assign patients to treatments, stratified by age above 65 years, insulin treatment within the past year and treatment centre in a 2 × 3 factorial design. The generation of the allocation sequence are in blocks, 1:1 for metformin placebo and 1:1:1 for insulin regimen. The computer provides full allocation concealment.

Outcomes

The primary outcome measure is the change in mean intima-media thickness of the common carotid arteries (CIMT) from trial entry to control at 18 months.

CIMT will be determined by using a GE Health Care Logic 9 ultrasound scanner (Milwaukee, Wisconsin, USA) with a linear probe M 12L 5–13 MHz. An arterial wall segment of approximate 10 mm will be imaged in a longitudinal view, located 5–10 mm proximal to the bifurcation and a minimum segment of 5 mm will be assessed. All images are saved as 4- to 6-second long dynamic movies. For each patient, the mean CIMT is imaged for the far wall of each common carotid artery. Scans are saved and transferred via DICOM to a computer for analysis. The images are analysed – blinded to interventions and other clinical information – with the MIA vascular research tools 5.0 (Medical Imaging Applications LLC, Coralville, IA, USA). The dynamic movie enables us to measure the arterial compliance and distensibility with the same software [27].

Secondary outcome measure comprises the following:

- Duration until occurrence of death, AMI, stroke or amputation estimated by an adjudication committee blinded to interventions;
- Duration until occurrence of cardiovascular deaths;
- Duration until occurrence of death, AMI, stroke, amputation, coronary revascularization or periphery revascularization;
- Change in average prandial glucose increment from 0 to 18 months;
- Hypoglycaemia and
- Any inadvertent medical episodes.

Tertiary outcome measures are changes from trial entry to control at 18 months in

- maximum intima-media thickness of the common carotid arteries (CIMT)
- plaque formation in the carotids
- cardiovascular biomarkers
- body composition estimated by dual X-ray absorptiometry (DEXA scanning)
- HbA1c.

Follow-up

The patients will be recruited at the various clinical centres and will be seen there every third month throughout the duration of the trial. The measurements of CIMT will be performed at a core centre (Steno Diabetes Center).

Sample Size and Power Calculation

Sample size calculations were based on detectable effect sizes using one-way ANOVA with pairwise comparisons (adjusting for five comparisons) for baseline to end-of-treatment changes for the primary outcomes across the six intervention groups. A sample size of 158 in each of the six groups (150 evaluable patients with a 5% drop out rate) has 85% power to detect a clinically relevant effect size of 0.018 mm of CIMT change. Based on a meta-analysis of seven trials with pravastatin vs. placebo [28] found a yearly statin-induced effect on CIMT of 0.012 mm (95% confidence interval 0.016–0.007), the standard deviation (s.d.) on CIMT progression in these trials being approximately 0.075 mm. For the sample size calculation, to detect or refute a metformin effect comparable to the effect of statins, we chose an 18-month metformin effect of 0.018 mm with a standard deviation on progression of 0.075 mm.

It is possible in practice to carry out a trial of a 2×3 factorial design with six intervention groups and a total of 900 patients, in which case the statistical power given by an alpha value of 0.01 (450 patients vs. 450 conservatively adjusting for five comparisons ad modem Bonferroni) will be 85% for proving or refuting the primary hypothesis of metformin being superior to placebo on CIMT.

It will be possible to analyse four additional comparisons with a power of either 80% (300 patients vs. 600 patients) or 64% (300 patients vs. 300 patients):

- Two insulin analogue regimens taken together vs. the 3rd insulin analogue regimen (600 patients vs. 300 patients); power = 80%.
- Insulin analogue regimen I vs. insulin analogue regimen II (300 patients vs. 300 patients), power = 64%.
- Insulin analogue regimen I vs. insulin analogue regimen III (300 patients vs. 300 patients), power = 64%.
- Insulin analogue regimen II vs. insulin analogue regimen III (300 patients vs. 300 patients), power = 64%.

The above comparisons assume that there is no interaction between the effects induced by metformin and by the insulin analogues.

Statistical Analysis

Two-way ANOVA will be used to compare baseline characteristics across the six groups. Two-way ANOVA (analysis of covariance, ANCOVA), including pairwise multiple comparisons (two sided), will be utilized to analyse baseline to end-of-treatment changes in outcomes for evaluable patients for each intervention. If data on the primary outcome measure, CIMT, are not normally distributed, transformation of data will be performed, for example by log transformation. Repeated measures ANOVA (ANCOVA) will be used for contrasting outcomes at baseline, 3, 6, 9, 12 and 18 months. Data sets on non-completing patients will be included in the data analyses on an intention-to-treat basis. In case of non-existent outcome measures (withdrawal, drop out and lost to follow-up), the pattern of missingness and the assumption of missingness at random (MAR) will be explored. If MAR is the most likely scenario, a multiple imputation in Statistical Analysis System (SAS) multiple imputation analysis (MIA) programme will be performed. Departure from the MAR criterion and the necessity for missing not at random (MNAR) models will be explored in sensitivity analysis.

According to International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials E9 [29] analysis of drug trials will primarily be carried out without adjusting for stratification and design variables (table 1), the latter being sex, myocardial infarction, coronary revascularization, Transient Cerebral Ischemia (TCI) or apoplexy, statin use and presence of Glutamic Acid Decarboxylase (GAD) antibody. Pursuant to the same recommendations, analyses will be carried out, making adjustments for entry CIMT and stratification variables including centre and a possible interaction between centre and intervention. Secondary analyses will include prognostically significant design variables (sex, myocardial infarction, coronary revascularization, TCI or apoplexy, statin use and presence of GAD antibody).

In all variance analyses, the transformed CIMT measurement at trial entry will be used as a covariate (ANCOVA) [30] for adjusting for CIMT differences between the intervention groups at baseline. All analyses will be conducted with adjustment for multiple comparisons with alpha at or below 0.01.

The secondary, composite outcome measure of duration until occurrence of one of the following events deaths, non-fatal AMI, non-fatal apoplexy or amputation will be studied by use of a proportional hazard analysis (Cox regression analysis). The analysis will be carried out primarily as univariate analyses with intervention group as factor and secondarily with correction for stratification and design variables (table 1).

The association between the postprandial glucose regulation and CIMT will be examined in a primary explorative analysis. The postprandial glucose regulation and CIMT will be studied using a multiple linear regression analysis having CIMT change (from 0 to 18 months) as dependent variable and the change in postprandial blood glucose reduction (from 0 to 18 months) as explanatory variable, with inclusion as well as exclusion of HbA1c, fasting blood glucose level and intervention arm into the

Table 1 Factors, variables of stratification and design variables to be analysed by analysis of covariances (ANCOVAs) in the CIMT trial

	Covariate	
Factor	**Stratification and baseline variable**	**Design variable**
+/− Metformin	CIMT at baseline	Sex
Type of insulin analogue regimen	Age	Previous myocardial infarction
	+/− Insulin treatment within the past year	Coronary revascularization
	Centre (Steno Diabetes Centre or else)	Transient Cerebral Ischemia (TCI) or apoplexy
	Centre * intervention	Statin use or not
		Presence or absence of Glutamic Acid Decarboxylase (GAD) antibody

CIMT, carotid intima-media thickness. Centre * intervention denotes the interaction between centre and effect of intervention.

model. Also, the association between the CIMT change (from 0 to 18 months) and the average postprandial blood glucose level change (from 0 to 18 months) will be tested in multiple linear regression analysis.

Study Organization and Timeline

The CIMT trial is entirely investigator initiated and controlled trial, which has obtained a grant by Novo Nordisk A/S. However, the CIMT investigators own the data and are committed to make all data publicly available regardless of results. The CIMT trial will be conducted in 10 clinical centres in the region of Copenhagen in Denmark. The Copenhagen Trial Unit coordinates randomization, data management and reporting of suspected unexpected serious adverse reactions.

Randomization commenced in May 2008 and is expected to be completed in September 2009. Follow-up will continue until March 2011, with publication of the primary results in 2011.

Implications and Conclusions

We believe that the CIMT trial will generate substantial and new knowledge concerning the extent to which metformin in combination with different insulin analogue regimens influences the control of diabetes and the progression of the atherosclerotic process. The CIMT trial was designed before the publication of results of the ADVANCE and ACCORD trials. The overall result of these two trials is that lowering of HbA1c to 6.0–6.5 does not seem to have an effect on progression of CVD. We still believe that CIMT is warranted as it addresses the question whether metformin should be continued or not when initiating insulin treatment and whether specific insulin regimens are advantageous. None of these questions is addressed in the two recent trials. As a consequence of the two trials, we decided to change the HbA1c target from 6.5% to 7.0%, and this was possible as the first patients were randomized late May 2008.

The CIMT trial will generate adequately powered prospective data to answer the question of whether treatment of postprandial hyperglycaemia with multiple daily injections of insulin in combination with basal insulin induces progression of atherosclerosis more than basal insulin alone. The results of the CIMT trial will furthermore unmask the extent to which additional long-term trials of different insulin treatment regimens with hard CVD outcomes should be initiated.

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