Online-Only Supplementary Material

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

Supplementary Table 1:

Number of serious adverse events according to metformin/placebo group

	Metformin No. of events	Placebo No. of events
Total no. of severe adverse events	81	72
1 Blood and lymphatic system disorders	0	1
2 Cardiac disorders	5	11
4 Ear and labyrinth disorders	0	1
6 Eye disorders	2	0
7 Gastrointestinal disorders	8	7
8 General disorders and administration site conditions	7	2
9 Hepatobiliary disorders	0	1
10 Immune system disorders	1	0
11 Infections and infestations	10	8
12 Injury, poisoning and procedural complications	3	3
13 Investigations	0	2
14 Metabolism and nutrition disorders	1	5
15 Musculoskeletal and connective tissue disorders	4	4
16 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	2
17 Nervous system disorders	3	1
19 Psychiatric disorders	4	3
20 Renal and urinary disorders	1	0
22 Respiratory, thoracic and mediastinal disorders	3	2
23 Skin and subcutaneous tissue disorders	3	4
25 Surgical and medical procedures	17	12
26 Vascular disorders	3	3

Supplementary Table 2:

Number of participants with serious adverse events according to metformin/placebo group

	Metformin	Placebo
	No. of patients	No. of patients
All severe adverse event	54	45
1 Blood and lymphatic system disorders	0	1
2 Cardiac disorders	5	9
4 Ear and labyrinth disorders	0	1
6 Eye disorders	1	0
7 Gastrointestinal disorders	7	5
8 General disorders and administration site conditions	7	2
9 Hepatobiliary disorders	0	1
10 Immune system disorders	1	0
11 Infections and infestations	10	8
12 Injury, poisoning and procedural complications	1	3
13 Investigations	0	2
14 Metabolism and nutrition disorders	1	3
15 Musculoskeletal and connective tissue disorders	4	3
16 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	1
17 Nervous system disorders	3	1
19 Psychiatric disorders	3	1
20 Renal and urinary disorders	1	0
22 Respiratory, thoracic and mediastinal disorders	3	2
23 Skin and subcutaneous tissue disorders	3	3
25 Surgical and medical procedures	13	11
26 Vascular disorders	2	2

Supplementary Table 3:

Number of adverse events according to metformin/placebo group

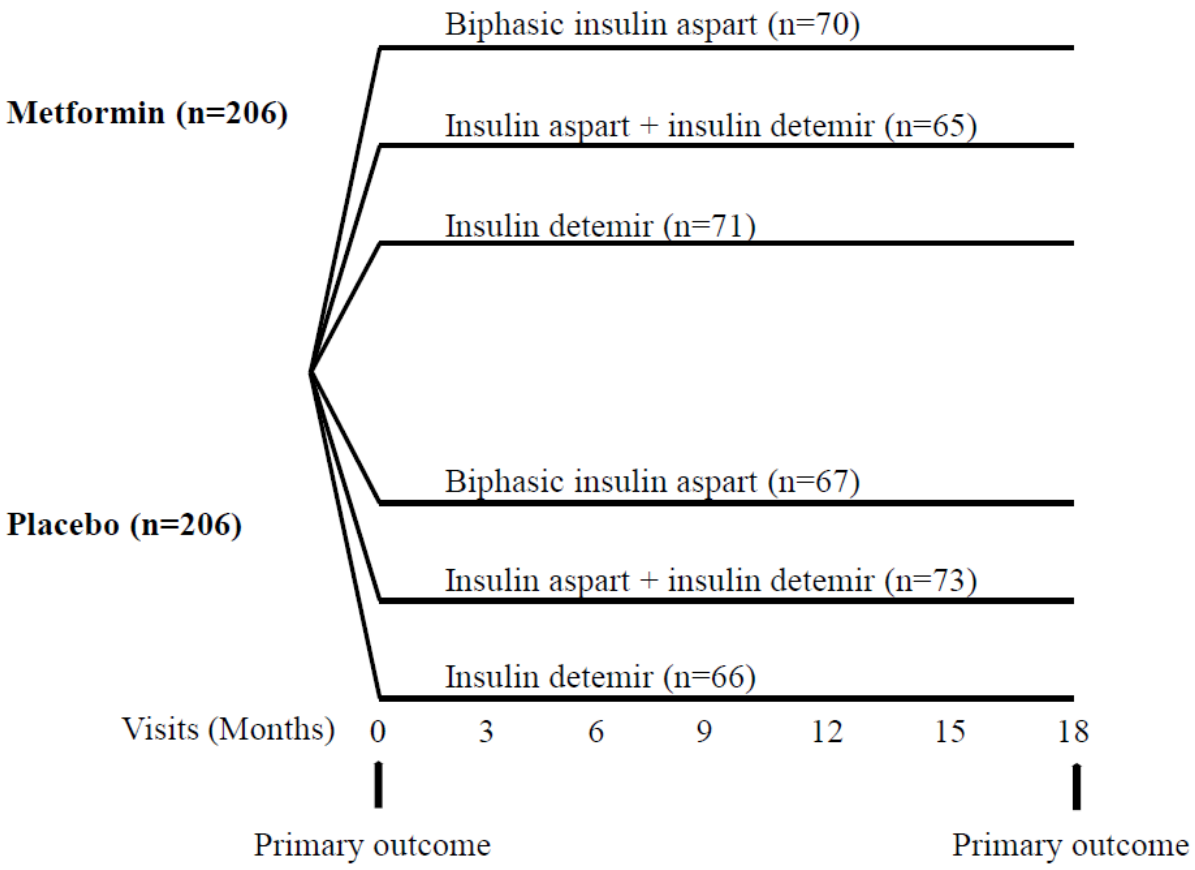
	Metformin	Placebo
	No. of events	No. of events
All adverse events	488	539
1 Blood and lymphatic system disorders	4	7
2 Cardiac disorders	7	8
4 Ear and labyrinth disorders	4	1
5 Endocrine disorders	2	0
6 Eye disorders	23	10
7 Gastrointestinal disorders	48	36
8 General disorders and administration site conditions	45	39
9 Hepatobiliary disorders	0	2
10 Immune system disorders	0	2
11 Infections and infestations	125	174
12 Injury, poisoning and procedural complications	23	18
13 nvestigations	13	14
14 Metabolism and nutrition disorders	18	20
15 Musculoskeletal and connective tissue disorders	61	84
16 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2
17 Nervous system disorders	23	38
19 Psychiatric disorders	7	7
20 Renal and urinary disorders	7	8
21 Reproductive system and breast disorders	7	2
22 Respiratory, thoracic and mediastinal disorders	11	14
23 Skin and subcutaneous tissue disorders	35	30
25 Surgical and medical procedures	14	16
26 Vascular disorders	10	7

Supplementary Table 4:

Number of participants with adverse events according to metformin/placebo group

	Metformin	Placebo
	No. of patients	No. of patients
All adverse events	169	155
1 Blood and lymphatic system disorders	4	6
2 Cardiac disorders	7	8
4 Ear and labyrinth disorders	4	1
5 Endocrine disorders	2	0
6 Eye disorders	19	9
7 Gastrointestinal disorders	37	27
8 General disorders and administration site conditions	39	34
9 Hepatobiliary disorders	0	2
10 Immune system disorders	0	1
11 Infections and infestations	79	89
12 Injury, poisoning and procedural complications	17	15
13 nvestigations	13	13
14 Metabolism and nutrition disorders	16	20
15 Musculoskeletal and connective tissue disorders	51	57
16 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2
17 Nervous system disorders	19	29
19 Psychiatric disorders	6	6
20 Renal and urinary disorders	5	7
21 Reproductive system and breast disorders	7	2
22 Respiratory, thoracic and mediastinal disorders	10	13
23 Skin and subcutaneous tissue disorders	30	22
25 Surgical and medical procedures	14	13
26 Vascular disorders	10	7

Supplementary Figure 1, Trial Design



Appendix 1: Guidelines for insulin dose titration

Guidelines for insulin dose titration in the CIMT trial (translated from the Danish version used in the trial).

The therapeutic goal is near-normalisation of HbA1c ≤7.0% taking the individual risk of hypoglycaemia into account.

The following algorithms are guidelines supporting the titration of insulin dose. It is at the investigators discretion to individual assessments.

Optimal therapeutic goal of fasting, pre-prandial and bedtime plasma glucose is <5.5 mmol/L.

It is at the investigators discretion to evaluate when the individual optimal insulin treatment is reached since the therapeutic goal might not be reachable in all participants.

After the initial titration all participants shall on a daily basis measure fasting plasma glucose and plasma glucose before insulin injections.

During the first 12 weeks of the trial, it is recommended that all participants have weekly telephone contact with the study nurse in order to discuss plasma glucose measurements, hypoglycaemic episodes and insulin titration. Subsequently, telephone contact is recommended every two to three weeks at the investigators discretio***Insulin titration guideline for insulin Levemir® once daily (bedtime).***

Initial dose of insulin in insulin naïve participants at trial entry is 0.2 IU/kg/day with injection in the thigh before bedtime.

Patients with insulin treatment at trial entry continue with insulin Levemir® 1:1 IU compared to the prior daily insulin dose .

Plasma glucose is measured daily before breakfast. The lowest measured plasma glucose is used to adjust insulin dose every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6,1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L the participant shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a fasting plasma glucose <5.5 mmol/L

NovoMix 30® initially once daily before dinner, with the possibility to increase to two or three injections a day.*

Initial dose of insulin in insulin naïve participants at trial entry is NovoMix 30® 0.2 IU/kg/day with injection in the thigh before dinner.

Patients with insulin treatment at trial entry continue with insulin NovoMix 30® 1:1 E compared to the prior daily insulin dose .

Plasma glucose is measured daily before breakfast. The lowest measured plasma glucose is used to adjust insulin dose every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6.1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L, the participant shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a fasting plasma glucose <5.5 mmol/L.

B. Introduction of a second dose of NovoMix 30®

When fasting plasma glucose is <5.5 mmol/L, before-dinner plasma glucose is measured.

If before-dinner plasma-glucose is >5.5 mmol/L, a second dose of 0.2 IU/kg NovoMix 30® is added in the morning.

Plasma glucose is measured daily before dinner. The lowest measured plasma glucose is used adjust insulin dose every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6.1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L, the participant shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a plasma glucose before dinner <5.5 mmol/L.

C. Introduction of a third dose of NovoMix 30®

If the therapeutic goal (defined as HbA1c<7.0%) is not reached with NovoMix 30® twice daily during the first three months, a third dose of 0.2 IU/kg NovoMix 30® is added before lunch.

Plasma glucose is measured daily before bedtime. The lowest measured plasma glucose is used adjust insulin dose every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6.1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L, the participant shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a plasma glucose before bedtime <5.5 mmol/L.

* Several previous studies have successfully titrated premixed insulin in patients with type 2 diabetes based on only fasting blood glucose levels to titrate insulin dose before dinner, and pre-dinner glucose to titrate the morning insulin dose, and in some patients also the lunchtime insulin dose (Lund et al, BMJ 2009). The major regulator of glycaemic control when using biphasic insulin is the long acting insulin component (70% of the insulin dose), which explains the use of the mentioned time points for glucose monitoring

Bedtime Levemir® in combination with Novorapid® before main meals

Initial dose of insulin in insulin naïve participants at trial entry is Levemir® 0.2 IU/kg/day with injection in the thigh before bedtime.

Patients with insulin treatment at trial entry continue with a daily dose of insulin Levemir® 1:1 E compared to the prior daily insulin dose .

50% of the total dose of insulin is injected as prandial insulin **NovoRapid®** and 50% is injected as bedtime Levemir®. The prandial insulin is injected as 35+30+35% before the three main meals taking individual eating habits into account.

The principle in the algorithm is initially to regulate fasting plasma glucose and subsequently pre-prandial and bedtime plasma glucose levels.

In this treatment regimen it is possible to treat post-prandial plasma glucose increase. The post-prandial plasma glucose levels should be regulated when the pre-prandial levels are optimised.

Plasma glucose is measured daily before breakfast. The lowest measured plasma glucose is used adjust insulin dose Levemir® **at bedtime** every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6.1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L the participant

shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a fasting plasma glucose <5.5 mmol/L.

B. Regulation of pre-prandial and bedtime plasma glucose levels.

Plasma glucose is regulated in the following order: before lunch, before dinner and bedtime according to the following:

Plasma glucose is measured daily before main meals and before bedtime. The lowest measured plasma glucose is used to titrate insulin **NovoRapid®** before the previous meal every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
< 4.4 mmol/L	- 2 IU
4.4 – 6.1 mmol/L	0
6.2 – 7.8 mmol/L	+ 2 IU
7.9 – 10 mmol/L	+ 4 IU
> 10 mmol/L	+ 6 IU

If one plasma glucose measure is ≤ 3.0 mmol/L the participant

shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a plasma glucose before meals and bedtime <5.5 mmol/L

C. Regulation of post-prandial plasma glucose

Plasma glucose is regulated in the following order: after breakfast, after lunch, after dinner according to the following:

Plasma glucose is measured daily one hour after meals. The dose of **NovoRapid® before the previous** meal is regulated every third day according to the following:

Plasma glucose	**Adjustment of insulin dose**
Mean PG < 4 mmol/L	- 2 IU
Two or more measures > 7 mmol/L	+ 2 IU

If one plasma glucose measure is ≤ 3.0 mmol/L the participant shall contact the study nurse or investigator in order to adjust insulin dose.

Goal is a plasma glucose one hour after meals < 7 mmol/L.

Appendix 2: Detailed description of ultrasound scan and analyses in the CIMT trial

After 10 minutes of rest in a supine position in a dark, quiet and temperature-controlled room, blood pressure was measured at the left upper arm. The scanning was performed using a General Healthcare (GE) logic 9 with a 9 linear (8 MHz) or a 12 linear (12 MHz) probe, however, the same probe was used for the individual participant. All images were obtained from the same ultrasound machine and performed randomly by two technicians. Initially, a rough cross sectional scanning was made from the proximal part of the common carotid artery throughout the bifurcation to the internal carotid artery and the external carotid artery to localize possible plaques or stenoses. Thereafter, a longitudinal scanning was made of the common carotid artery with storage of a dynamic sequence of 4-6 seconds for the measurement of carotid intima-media thickness. For the border detection and calculations, we used specialized software (vascular tools 5, Medical Imaging Applications, Iowa, United States of America). The region of interest was defined as a segment of the far wall in common carotid artery devoid of focal plaques and spanning 5-10 mm with a centre 10 mm proximal to the bulb. The software identifies the lumen/intima and the media/adventitia borders and calculates the distance in between, i.e. the carotid IMT. The resolution of the ultrasound picture is 10 pixels/ mm. The frequency of the picture is 15 pictures per second during five seconds. Thus, the final average carotid IMT on a 10 mm segment of the vessel wall is based on approximately 7,500 automated calculations during the 5 seconds. The mean carotid IMT was calculated as the average of the mean intima-media thickness of the left and right common carotid artery. Maximum carotid IMT was likewise defined as the average of the maximum IMT from the left and right common carotid artery. Carotid plaque was defined as carotid IMT >1.5mm, or focal encroachment into the lumen of >0.5mm, or focal increment of >50% of the carotid IMT compared to the surrounding area. Carotid plaques were quantified on left and right side in each of the following carotid regions: Common, external, internal and bulb and were thereafter summarized to the total number of plaques 1-5 or >5. The cross-sectional intima-media area was calculated from the formula: $\Pi*(LD/2+IMT)^2-\Pi*(LD/2)^2$, where LD is the lumen diameter and IMT is the mean intima-media thickness (mm). Relative compliance (cross sectional distensibility, $mmHg^{-1}$) of the common carotid artery was automatically calculated as a measure of the change in vessel volume from systole to diastole calculated from the equation: (radius in $systole^2$ – radius in $diastole^2$) / (radius in $diastole^2$ x puls pressure) where high/increased values are beneficial for the haemodynamic system. Incremental elastic modulus (IEM, mmHg) reflects the intima-media layers tendency to be deformed elastically where low/reduced values are beneficial for the haemodynamic system.