Pharmacological treatment of the pathogenetic defects in Type 2 Diabetes. The randomized multi-centre South Danish Diabetes study (SDDS)

Short running title: The South Danish Diabetes Study

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**Objective:** To determine the effect of treatment with insulin Aspart as compared to NPH insulin, together with metformin/placebo and rosiglitazone/placebo. The hypothesis was that combined correction of major pathogenetic defects in type 2 diabetes would result in optimal glycemic control.

**Research Design and Methods:** A 2-year investigator driven, randomized, partly placebo controlled, multicenter trial in 371 patients with type 2 diabetes on at least oral antiglycemic treatment. Patients were assigned to one of eight treatment groups in a factorial design with insulin aspart at mealtimes vs. NPH insulin once daily at bedtime, metformin twice daily vs. placebo, and rosiglitazone twice daily vs placebo. Main outcome measurement: change in HbA1c.

**Results:** HbA1c decreased more in patients treated with insulin aspart compared to NPH (-0.41 ± 0.10%, p<0.001). Metformin decreased HbA1c compared to placebo (-0.60 ± 0.10%, p<0.001) as did rosiglitazone (-0.55 ± 0.10%, p<0.001). Triple therapy (rosiglitazone, metformin and any insulin) resulted in a greater reduction in HbA1c than rosiglitazone+insulin (-0.50 ± 0.14%, p<0.001) and metformin+insulin (-0.45±0.14%, p<0.001). Aspart was associated with a higher increase in body weight (1.6±0.6kg, p<0.01) and higher incidence of mild daytime hypoglycemia (4.9±7.5 vs 1.7±5.4 number/person/year, p<0.001) as compared to NPH.

**Conclusions:** Insulin treatment of postprandial hyperglycemia results in lower HbA1c than treatment of fasting hyperglycemia, at the expenses of higher body weight and hypoglycemic episodes. However, insulin therapy has to be combined with treatment of both peripheral and liver insulin resistance in order to normalize blood glucose and in this case the insulin regiment is less important.

**Trial registration:** ClinicalTrials.gov number NCT00121966.

Only a few long-term studies have focused on different insulin treatment modalities and the blinded combination with different oral antidiabetic drugs. Theoretically the best anti-glycemic treatment is to aim at restoring the main pathophysiological defects in type 2 diabetes: decreased first phase insulin secretion, peripheral insulin resistance and elevated hepatic gluconeogenesis. These defects may theoretically be partly corrected pharmacologically by a rapid-acting insulin analogue before meals, mimicking the lacking postprandial insulin peak; by an insulin sensitizer improving peripheral insulin action; and by metformin reducing hepatic glucose production (1). The South Danish Diabetes Study (SDDS) is an investigator driven, 2-year, randomized and controlled clinical trial testing the hypotheses that; 1) the more physiological insulin profile obtained with insulin aspart treatment at meals (without long-acting insulin at night) is more effective than the conventional use of NPH insulin given once daily at bedtime; 2) addition of metformin or rosiglitazone to insulin treatment will further improve the glucose control and; 3) combination of insulin, metformin and rosiglitazone – triple therapy – will result in the most optimal glycemic control.

**RESEARCH DESIGN AND METHODS**
Subjects. Patients aged 30 to 70 years with type 2 diabetes mellitus (T2D) were included at eight hospital centers in the Southern Region of Denmark. Eligible patients had the following characteristics: BMI > 25 kg/m² and fasting plasma C-peptide > 300 pmol/l, treatment for at least three months with stable doses of oral antidiabetic medications and/or insulin and HbA1c > 7.0%. Prior insulin treatment could be any insulin regimen but most were treated with long-acting insulin. The exclusion criteria were: congestive heart failure, impaired renal function and known intolerance to metformin or rosiglitazone and/or treatment with glitazones less than 30 days before randomization.

Study design. Four hundred and fifty patients were included. After a four-week run-in period all 371 eligible patients were randomized to one of eight treatment groups in a factorial design with NPH insulin vs insulin aspart, metformin vs placebo and rosiglitazone vs placebo (Figure 1). After a three-month insulin titration period patients were followed every three months for two years.

Intervention. All prior antidiabetic treatments were stopped. Patients allocated to NPH insulin at bedtime measured fasting blood glucose (FBG) every day and received a starting dose of 12 IU. Patients already on insulin received 50% of their prior total daily dose. In a treat-to-target algorithm insulin dose was increased by 2 IU if FBG>5.6, 4 IU if FBG>8.0 and 6 IU if FBG>12.0 mmol/l on three consecutive days until FBG was below 5.5 mmol/l and HbA1c<6.5% provided no unacceptable hypoglycemic episodes.

Patients allocated to insulin aspart measured postprandial (PP) blood glucose 3 times daily 90 minutes after each main meal and received a starting dose of 4 IU just before each main meal. Patients already on insulin received 50% of their prior total daily dose divided into three doses. In a treat-to-target algorithm insulin dose at each meal was increased by 1 IU if PP BG≥7.5, 2 IU if PP BG≥9.0, 3 IU if PP BG≥11.0 mmol/l on three consecutive days until postprandial blood glucose was below 7.5 mmol/l and a HbA1c <6.5% provided no limiting hypoglycemic episodes.

After a three-month intensive insulin titration period, patients were instructed to continue using the algorithm but daily BG glucose monitoring was not requested if the treatment goals were achieved.

Metformin or placebo was given from the start of the study as one tablet of 500 mg twice daily during the first four weeks succeeded by two tablets twice daily, and rosiglitazone or placebo was given as one tablet of 4 mg once daily in the first eight weeks succeeded by one tablet twice daily.

An increase of HbA1c by more than 2.0% (absolute) or HbA1c exceeding 12.0% (absolute), measured twice over a 6 months period were considered treatment failures.

Biochemical and clinical measurements. Glycated hemoglobin (HbA1c) was measured every three months.

Patients made daily capillary blood glucose (BG) monitoring (One Touch Ultra, Lifescan) and performed two 8 point 24-hour glucose profiles before each visit.

Safety assessments. Any adverse event was recorded. Hypoglycemic episodes were registered by the patients every day in a diary and were defined as either mild (BG >2.8 mmol/l and symptoms consistent with hypoglycemia) or moderate (BG <2.8 mmol/l with or without symptoms). Serious hypoglycemia was defined as any hypoglycemic episode requiring assistance.

Protocol oversight. The protocol was in accordance with the Declaration of Helsinki and approved by the regional committee on Biomedical Research Ethics (M-2417-02). GCP monitoring was performed by the local GCP-unit and a contract company. Statistical analysis was performed by an independent statistician. The statistical analysis plan was completed before the database was locked and
un-blinded. Safety data was reviewed un-
blinded during the study by an independent
academic diabetologist. The randomization
code was developed by an independent
statistician using a computer random number
generator to select random blocks of 8.
Randomization to insulin type was open
whereas allocation to other treatments was
double-blinded.

**Sample size.** The primary outcome variable
was HbA1c. Assuming a minimal relevant
difference between the two insulin treatment
arms of 0.4 % and a standard deviation of
1.15, a total of 176 in each of the pooled
insulin treatment groups were calculated as
necessary to provide the study with 90%
power to detect a difference of this magnitude
(p<0.05). Assuming a dropout rate of 10%, a
total of around 400 subjects were planned to
be included.

**Statistical analysis.** The factorial design of
the study allowed us to compare the effect of
each component in the antidiabetic treatment
evaluated but not to compare every eight
treatment groups with each other. In
accordance with the hypothesis we compared
insulin aspart with NPH insulin, the effect of
adding metformin and/or rosiglitazon to
insulin treatment and with special attention to
the effect of triple therapy
(insulin+metformin+rosiglitazon). All data
are presented as mean ± SD or SEM.
Statistical analysis was on an intention-to-
treat basis and last observation carried
forward (LOCF). A per protocol analysis for
the primary endpoint was also performed. The
efficacy analysis (HbA1c) was performed by
analysis of covariance on changes from
baseline to the mean of HbA1c for 12 – 24
months (inclusive) with the three treatments
and centre as fixed main effects and baseline
HbA1c value as a covariate. Patient was a
random effect in the model. First order
interactions and each of the following
baseline covariates were also included as
fixed effects in the statistical model: fasting
plasma C-peptide, interaction between fasting
plasma C-peptide and treatment, previous
insulin use. Treatment differences in the
number of patients with HbA1c ≤7.0% were
tested using logistic linear regression, with the
three treatments and their interactions
included in the model. Plasma glucose
profiles were analyzed by a repeated
measures analysis of variance, performed
after logarithmic transformation. Hypoglycemic episodes were analyzed using
a generalized linear model based on the
negative binomial distribution. Number of
patients experiencing at least one
hypoglycemic episode were compared with
the groups using Fishers exact test.

**RESULTS**

**Patient characteristics.** There were no
clinical important differences in baseline
demographic and clinical characteristics
between treatment groups in the study
population (Table 1).

**Glycemic control.** The overall difference
between the reduction in HbA1c between the
aspart and NPH groups (N = 175 vs 182) was
-0.41 ± 0.10 %-point (p<0.001), i.e. insulin
aspart was associated with a larger reduction
in HbA1c than observed with NPH insulin.
Moreover, in all patients metformin vs
placebo treatment (N = 179 vs 178) was
associated with a decrease in HbA1c of -0.60 ±
0.10 % (p<0.001) and rosiglitazone vs
placebo treatment (N= 179 vs 178) with a
decrease of –0.55 ± 0.10 % (p<0.001). When
only the per protocol population was
examined, similar results were observed.
As illustrated in Figure 2 and Table 2,
HbA1c decreased in all 8 study groups but
most during addition of oral antidiabetics to
insulin. There was no difference between the
two triple therapy groups (ASP vs NPH plus
metformin and rosiglitazone)(P=0.15). Triple
therapy, with any insulin, resulted in the
greatest reduction in HbA1c as compared to
any insulin plus placebo (-1.14 ± 0.13 %,
p<0.001), any insulin plus rosiglitazone (-0.50 ± 0.14 %, p<0.001) and any insulin plus metformin (-0.45 ± 0.14 %, p<0.001).

The percentage of patients reaching the HbA1c target of <7.0% in all patients were: aspart vs NPH (48 vs. 42%, p=0.25), metformin vs placebo (56 vs. 34%, p<0.001) and rosiglitazone vs placebo (56 vs. 34%, p=0.002). The percentage reaching the same goal in the two triple therapy groups, aspart vs. NPH was 64 vs 67%, (p=0.15).

Self-monitored plasma glucose profiles were significantly lower using insulin aspart vs NPH insulin (p=0.005), metformin vs placebo (p<0.001) and rosiglitazone vs placebo (p<0.001) (Supplementary Fig. 1 in the online appendix available at http://care.diabetesjournals.org).

**Insulin dose.** Insulin dose was highest in the groups treated by insulin alone, whereas addition of either metformin or rosiglitazone resulted in a decrease in total daily insulin dose and addition of both metformin and rosiglitazone resulted in the lowest insulin dose (Table 2).

**Hypoglycemia.** Overall, more patients using insulin aspart reported at least one hypoglycemic episode as compared to the patients using NPH insulin (160 vs 137, p=0.005), with no difference between the metformin and placebo groups (143 vs 154, NS) or between the rosiglitazone and placebo groups (150 vs 147, NS).

During the last year of intervention, treatment with insulin aspart was associated with more total daytime hypoglycemic episodes as compared to NPH insulin (6.7 ± 9.9 vs. 1.9 ± 5.7, p<0.001). However, the total number of nocturnal hypoglycemic episodes was higher in the NPH insulin group as compared to the aspart group (3.0 ± 6.3 vs. 0.5 ± 2.1, p<0.001). During the entire intervention period, 8 patients in the NPH insulin group experienced 8 episodes of severe hypoglycemia and 11 patients in the aspart group experienced 13 episodes.

**Body weight.** Body weight increased in all treatment groups (Table 2). Overall, insulin Aspart was associated with an increase in body weight of 1.6 ± 0.6 kg (p=0.009) as compared to NPH insulin, rosiglitazone with an increase of 2.3 ± 0.6 kg (p<0.001) as compared to non-rosiglitazone treatment and metformin with a decrease in body weight of 2.8 ± 0.6 kg (p<0.001) as compared to non-metformin treatment.

**Adverse events.** When the NPH and insulin aspart groups were compared, statistically significant more adverse events (AE) were found in the insulin aspart group (861 vs 723) (p<0.003). There was no statistical significant differences between specific AE between the two groups and no difference in number of serious adverse events (SAE) was found (51 vs 56) or death (4 vs 0, Figure 1). No difference in adverse events, either in AE or in SAE was found comparing the metformin and placebo group (SAE: 53 vs 54) or the rosiglitazone and placebo group (SAE: 54 vs 56). (The details of the specific AE’s can be found in the Supplementary, Table 1).

**DISCUSSION**

**Effect of insulin treatment on blood glucose control.** The study provide evidence that mono-therapy with NPH insulin at bedtime is not an optimal way of treating hyperglycemia in T2D although this treatment has been recommended until recently (2,3). It could be argued that a long-acting insulin analogue would have performed better, but in the LANMET treat-to-target trial comparing NPH insulin and insulin glargine (4), the two insulin treatments combined with metformin gave exactly identical HbA1c values.

Treatment with insulin aspart resulted in better blood glucose control than NPH insulin even though aspart was not combined with any basal insulin. The difference between aspart and NPH treatment on HbA1c disappeared when combined with metformin or both metformin and rosiglitazone. The
benefit of prandial insulin treatment was also found during the first year of the 4T study (5) but disappeared in the 2 year follow up (6) when basal – bolus insulin treatments were combined.

Recently another study has shown a non-significant difference in favor of insulin Lispro as compared to insulin glargine of approximately 0.2% in HbA1c (7), which is supported by an older study also comparing insulin Lispro with insulin Glargine and showing a significant reduction in HbA1c of 0.8% in the prandial insulin Lispro group (8). It has been shown that postprandial hyperglycaemia is an important determinant for the level of HbA1c especially the closer the HbA1c is to the treatment goal (9), supporting that treatment aimed at replacing first phase insulin secretion is important. Furthermore, an advantage of the solely prandial insulin regiments is that during the night patients are only covered by endogenous insulin production and therefore do not develop nocturnal hypoglycemia (10).

**Effect of OHA treatment on blood glucose control.** Both metformin and rosiglitazone as add-on to insulin treatment improved the metabolic control significantly and lowered the insulin dose indicating that it is important not only to give insulin, but also to improve insulin action in peripheral tissues and in the liver. Several previous studies have addressed the issue of combining insulin and metformin treatment and have indicated a clear advantage of doing so (11-15).

Most studies on combination treatment with glitazone and insulin have found an improvement in glycemic control compared to insulin given in monotherapy (15-19) and moreover glitazones also have an insulin sparing effect (15-18). However, the combination treatment is associated with an increase in body weight (15-19).

**Effect of triple therapy treatment on blood glucose control.** The most optimal treatment with respect to glycemic control in our study was triple therapy using insulin, rosiglitazone and metformin. Around 66% of our patients treated with triple therapy reached the HbA1c target of <7.0%. Such a high proportion of responders have only rarely been achieved in other randomized trials of insulin treatment in type 2 diabetes besides in the advanced insulin regiments groups in the 4T trial (6). The same combination therapy has been investigated in a few short term studies previously (10,20-23). The triple concept gave identical results no matter what insulin regimen was used. The reason for this seems to be that insulin Aspart only replaces first phase insulin secretion and NPH insulin only basal insulin thus not covering the full 24-hour period adequately. Based on the 4-T follow-up study (6) it may be speculated that the combined effect of parandial aspart and basal NPH insulin would have been the best treatment.

**Hypoglycemia.** The overall numbers of clinical relevant hypoglycemic episodes were low, being comparable to the number reported in the 4T trial (5). Despite the surplus of hypoglycemic episodes in the insulin aspart group the majority of episodes were at daytime which may be more acceptable than nocturnal episodes seen more often in the NPH insulin group. Moreover, it can be speculated if the measurements of postprandial glucose concentration trice daily in the aspart groups made this group more prone to register hypoglycemic episodes during the day.

**Body weight.** It is well-known that improvement in blood glucose control often will increase body weight. Insulin treatment in combination with glitazones may result in more weight gain than other treatments (24). However, interestingly if we compared the weight gain using triple therapy with insulin, metformin and rosiglitazone, it was comparable to that observed with insulin treatment alone as also seen in the 4T study (5).
Adverse effects. There is no clear explanation for the increased number of AE found in the aspart treated groups. It was seen in all system organ classes but not in the number of SAE or death. All AE was noted by the patients in their diabetes diary and it may be speculated if the trice daily measurement and notation of BG made them more prone to report AE as compared to the NPH group only measuring FBG.

Recently the ACCORD, ADVANCE and VADT studies have been published showing no benefit in relation to reduction in risk of cardiovascular disease with improvements in glycemic control. It is important to realize, that our study was not a study designed to address this issue. Moreover, it seems from the recent follow up study of the UKPDS (25) that normalization of glycemic control should be obtained when the diagnose of Type 2 diabetes is made, and further that the benefits of the improvement in glycemic control were maintained many years following the study intervention (25).

CONCLUSION
Treatment of postprandial hyperglycemia with insulin aspart results in lower HbA1c than treatment of fasting hyperglycemia with NPH insulin, but with more side effects. For optimal treatment insulin has to be combined with treatment of both peripheral and liver insulin resistance and in this case the choice of insulin regimen is less important.

Author Contributions. JG planned study, researched data, wrote manuscript, JEH planned study, researched data, wrote manuscript, EG planned study, researched data, edited manuscript, HJ planned study, researched data, edited manuscript, TBH planned study, researched data, edited manuscript, CC researched data, edited manuscript, KY planned study, researched data, edited manuscript, HG planned study, researched data, edited manuscript, HMH planned study, researched data, edited manuscript, VV planned study, researched data, edited manuscript, JH planned study, researched data, edited manuscript, HBN planned study, researched data, wrote manuscript.

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REFERENCES


TABLE 1. Baseline clinical characteristics of the study population.

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<th>Treatment group</th>
<th>NPH + plac</th>
<th>NPH + met</th>
<th>NPH + rosi</th>
<th>NPH + both</th>
<th>NPH total</th>
<th>ASP + plac</th>
<th>ASP + met</th>
<th>ASP + rosi</th>
<th>ASP + both</th>
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<td>45</td>
<td>46</td>
<td>46</td>
<td>183</td>
<td>48</td>
<td>45</td>
<td>47</td>
<td>48</td>
<td>188</td>
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<td>19/26</td>
<td>18/28</td>
<td>16/30</td>
<td>66/117</td>
<td>25/23</td>
<td>17/28</td>
<td>20/27</td>
<td>13/34</td>
<td>76/112</td>
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<td>Age (yr)</td>
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<td>57.3 ± 8.9</td>
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<td>Diabetes duration (yr)</td>
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<td>8.1 ± 5.3</td>
<td>8.2 ± 5.2</td>
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<td>8.7 ± 4.5</td>
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<td>9.0 ± 5.8</td>
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<td>Body weight (kg)</td>
<td>100.2 ± 19.8</td>
<td>105.1 ± 17.7</td>
<td>100.9 ± 16.5</td>
<td>101.1 ± 19.3</td>
<td>102.1 ± 18.3</td>
<td>98.3 ± 16.6</td>
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<td>BMI (kg/m2)</td>
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<td>34.4 ± 7.0</td>
<td>34.5 ± 6.3</td>
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<td>32.9 ± 4.4</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.7 ± 1.3</td>
<td>8.9 ± 1.2</td>
<td>8.7 ± 1.2</td>
<td>8.5 ± 1.1</td>
<td>8.7 ± 1.3</td>
<td>8.5 ± 1.2</td>
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<td>F-P glucose (mM)</td>
<td>11.2 ± 2.6</td>
<td>11.3 ± 2.8</td>
<td>10.5 ± 2.4</td>
<td>10.2 ± 2.6</td>
<td>10.8 ± 2.6</td>
<td>10.7 ± 2.5</td>
<td>10.0 ± 2.3</td>
<td>9.9 ± 2.1</td>
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<tr>
<td>F-S C-peptide (pM)</td>
<td>1063 ± 495</td>
<td>1115 ± 505</td>
<td>1026 ± 554</td>
<td>1099 ± 548</td>
<td>1076 ± 523</td>
<td>1070 ± 528</td>
<td>967 ± 460</td>
<td>975 ± 440</td>
<td>1000 ± 467</td>
<td>1003 ± 474</td>
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</table>

*No patients had ever received glitazone or DDP-4 inhibitor treatment prior to the study.
Values are mean ± SD. NPH, Neutral Protamine Hagedorn Insulin (Insulatard, Novo Nordisk); ASP, Insulin aspart (NovoRapid, Novo Nordisk); plac, placebo; met, metformin; rosi, rosiglitazone; both, metformin + rosiglitazone. F-P glucose: Fasting plasma glucose concentration; F-S C-peptide: Fasting C-peptide concentration; SU: Sulfonylurea
**TABLE 2.** Observed HbA1c, percentage of patients with HbA1c ≤ 7.0%, fasting venous plasma glucose concentration, insulin dose, body weight and hypoglycemic episodes following 2 years of treatment.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>NPH + plac</th>
<th>NPH + met</th>
<th>NPH + rosi</th>
<th>NPH + both</th>
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<th>ASP + met</th>
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<tr>
<td><strong>HbA1c (%)</strong></td>
<td>8.3 ± 1.4</td>
<td>7.6 ± 1.3</td>
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<td>6.8 ± 0.9</td>
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<td><strong>HbA1c ≤ 7% (%)</strong></td>
<td>20</td>
<td>42</td>
<td>39</td>
<td>67</td>
<td>24</td>
<td>51</td>
<td>52</td>
<td>64</td>
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<td><strong>Fasting glucose (mM)</strong></td>
<td>7.3 ± 2.5</td>
<td>6.6 ± 2.0</td>
<td>6.6 ± 2.6</td>
<td>5.7 ± 1.5</td>
<td>12.2 ± 3.9</td>
<td>9.6 ± 3.1</td>
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<td><strong>Insulin dose (IU)</strong></td>
<td>100.4 ± 64.6</td>
<td>80.1 ± 55.5</td>
<td>55.3 ± 41.1</td>
<td>39.0 ± 34.4</td>
<td>89.6 ± 58.9</td>
<td>61.2 ± 38.6</td>
<td>53.6 ± 41.3</td>
<td>46.7 ± 34.7</td>
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<td><strong>Body weight (kg)</strong></td>
<td>105.5 ± 20.2</td>
<td>108.0 ± 19.6</td>
<td>108.5 ± 21.1</td>
<td>105.7 ± 20.9</td>
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<td><strong>Hypoglycemia</strong></td>
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<td><strong>Any (%)</strong></td>
<td>35 (76%)</td>
<td>33 (73%)</td>
<td>37 (80%)</td>
<td>32 (70%)</td>
<td>43 (91%)</td>
<td>36 (82%)</td>
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<td>Mild</td>
<td>2.3 ± 8.2</td>
<td>1.0 ± 2.7</td>
<td>1.4 ± 3.9</td>
<td>2.0 ± 4.8</td>
<td>10.1 ± 12.2</td>
<td>9.1 ± 10.5</td>
<td>9.2 ± 14.6</td>
<td>10.4 ± 12.4</td>
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<tr>
<td>Moderate + severe</td>
<td>0.4 ± 1.4</td>
<td>0.3 ± 1.1</td>
<td>0.2 ± 0.6</td>
<td>0.3 ± 1.2</td>
<td>3.1 ± 6.3</td>
<td>2.9 ± 4.9</td>
<td>3.6 ± 10.9</td>
<td>3.9 ± 7.7</td>
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<tr>
<td>Mild</td>
<td>2.6 ± 8.1</td>
<td>1.1 ± 2.9</td>
<td>1.9 ± 5.8</td>
<td>1.1 ± 2.9</td>
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<td>0.3 ± 0.9</td>
<td>0.1 ± 0.4</td>
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<td>0.2 ± 0.7</td>
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<td>1.5 ± 2.6</td>
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<td>1.4 ± 4.0</td>
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<tr>
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<td>2.8 ± 6.1</td>
<td>2.8 ± 4.8</td>
<td>3.2 ± 5.2</td>
<td>4.3 ± 10.0</td>
<td>1.4 ± 3.1</td>
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<tr>
<td>Moderate + severe</td>
<td>0.5 ± 1.9</td>
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<td>1.1 ± 3.0</td>
<td>1.1 ± 3.0</td>
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<td>0.2 ± 0.6</td>
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<td><strong>Year 2</strong></td>
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<tr>
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<td>2.8 ± 4.5</td>
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<tr>
<td>Moderate + severe</td>
<td>1.1 ± 2.9</td>
<td>0.5 ± 1.3</td>
<td>1.3 ± 3.0</td>
<td>0.4 ± 1.2</td>
<td>0.2 ± 0.6</td>
<td>0.2 ± 0.7</td>
<td>0.1 ± 0.3</td>
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</table>

Values are mean ± SD. Hypoglycemic episodes were recorded as the total number of episodes in the first and second year of the intervention period. Moderate episodes were those with either plasma glucose concentrations below 2.8 mM or when assistance from another person was needed. Unit for daytime and nighttime hypoglycemic episodes is number/person/year.

NPH, Neutral Protamine Hagedorn Insulin (Insulatard, Novo Nordisk); ASP, Insulin aspart (NovoRapid, Novo Nordisk); plac, placebo; met, metformin; rosi, rosiglitazone; both, metformin + rosiglitazone
**Figures legends**

**Fig. 1.** Enrolment and outcomes. The number of participants enrolled in the study. The intention-to-treat (ITT) population included 369 patients as 2 were withdrawn before first efficacy evaluation. The per-protocol-population included 251 patients.

**Fig. 2.** Mean (±SEM) observed HbA1c values during the 2 years intervention period in patients randomized to treatment with either NPH insulin (black symbols) or insulin aspart (open symbols) in combination with either placebo (A, p<0.001), metformin (B, p=0.15), rosiglitazone (C, p<0.02) or metformin and rosiglitazone (D, p=0.15).
Figure 2