Silvestre L, Bradley C and Witthaus E (2003) Improved treatment satisfaction and perceived metabolic control with insulin glargine, regardless of whether injected before breakfast, dinner or bedtime, in patients with Type 1 diabetes. *Diabetes* **52** Suppl 1 A456, Abstract 1977-PO.

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unit (ICU) showed that intensive treatment with insulin improves outcome. However, two-thirds of these patients were admitted after cardiac surgery and hence, these results may not be applicable to other patients in ICUs. We conducted a prospective study of patients admitted to our general ICU admitting non-cardiac surgery and medical patients, to document the relationship between blood glucose concentrations and outcome. Eighty five patients were studied but the final analysis was restricted to 77 non-diabetic patients. Eighteen patients were treated with insulin. Patients were divided into two groups on the basis of their maximum blood glucose level prior to insulin treatment with value of 200 mg/dL chosen as the cut-off point as it would be diagnostic of diabetes mellitus. There were 42 patients with levels above and 35 patients with levels below 200 mg/dL. The final outcome measures were mortality on ICU and the length of ICU stay. Patients with higher glucose concentrations had a 3.6 fold (95% CI 1.4 to 8.9) higher risk of death on ICU and significantly longer length of ICU stay (table 1). Our study shows that hyperglycemia in critically ill patients is associated with poor outcome.

Blood Glucose versus ICU Mortality and Length of Stay.

Outcome	Glucose > 200 mg/dL (n=35)	Glucose < 200 mg/dL (n=42)	p value
Death on ICU - no./ total no. (%)	15/35 (43)	5/42 (12)	0.0035
Median length of ICU stay - days (95% CI)	6 (6.9 - 14.3)	2 (2.3 - 6.6)	0.0004

1976-PO

Basal Insulin Therapy in Type 2 Diabetes: A Prospective 18 Month Comparison of Insulin Glargine and NPH Insulin in Patients with a Multiple Injection Regimen

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The UKPDS has established that long term tight metabolic control delays the onset and progression of diabetic micro- and macrovascular complications. To meet glycemic goals multiple injection regimens (ICT) are one therapeutic option.

Up to date only marginal long term data is available about the long-acting insulin analogue glargine (IG). We chose a prospective long term approach over 18 months to determine the safety and efficacy of IG compared with NPH insulin (NPH) in type 2 diabetic patients.

We analysed a subgroup of patients treated with an ICT and compared IG once daily with NPH twice daily in this single centre, open-label study. Up to date 52 (IG) respectively 51 (NPH) patients completed the trial. Preprandial insulin was a short acting insulin analogue.

Age, duration of diabetes (dod) and C-peptide (C-p) did not differ significantly in both groups (IG group: age 60.8 years, dod: 14.6 years, mean fasting C-p: 0.78 ng/ml, NPH group: age 61.9 years, dod: 15.2 years, fasting C-p: 0.82 ng/ml). After 18 months of treatment the HbA1c level improved only in the IG group significantly from 7.4% to 7.0% (means ± SD: -0.39±0.8, $p<0.003$) compared to the NPH group (HbA1c from 7.4% to 7.2%, means ± SD: -0.20±0.78, $p<0.06$). We found no significant increase of the daily insulin doses (IG group: final dose: 0.29 IU/kg, start dose: 0.28 IU/kg, NPH group: final dose: 0.38 IU/kg, start dose: 0.35 IU/kg). Also the preprandial insulin doses did not differ significantly. Both groups did no show a significant increase of the mean body-mass-index. A significantly lower number of symptomatic hypoglycemia in the IG group was documented, no severe hypoglycemias were detected.

In an 18 months clinical trial patients with type 2 diabetes treated with a multiple injection regime, IG once daily resulted in a significant improvement of metabolic control and no significant changes in body weight and insulin dose. IG provides a clinical advantage over NPH also with respect to the incidence of mild hypoglycemia.

1977-PO

Improved Treatment Satisfaction and Perceived Metabolic Control with Insulin Glargine, Regardless of Whether Injected before Breakfast, Dinner or Bedtime in Patients with Type 1 Diabetes

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Insulin glargine (LANTUS®) is a once-daily basal insulin analog that facilitates A1c targets <7%. A recent study showed that glargine, plus prandial insulin, is effective, injected either before breakfast, before dinner or at bedtime in patients with type 1 diabetes. The effect of these administration times on treatment satisfaction and perceived metabolic control is presented. In this open-label, randomized, parallel group, multicenter, 24-week study, 332 of the 378 treated patients completed the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) at baseline and study endpoint. At baseline, 275 (72.8%) patients in the clinically evaluated population had an injection time preference (118 [42.9%]: breakfast, 28 [10.2%]: dinner, 105 [38.2%]: bedtime); 24 (8.7%) preferred a combination. Mean (± SD) baseline treatment satisfaction scores, when most patients were using NPH insulin, were 27.8 ± 5.0, 27.4 ± 5.5 and 28.1 ± 5.3 in the breakfast, dinner and bedtime groups, respectively, and increased in all groups from baseline to endpoint (1.4, $p=0.079$; 2.5, $p=0.0002$; 1.8, $p=0.009$, respectively; paired t-test). The largest increases came from a change in the DTSQ convenience score (breakfast: 0.5, $p=0.005$; dinner: 0.8, $p=0.0001$; bedtime: 0.7, $p=0.0001$) and 'wish to continue' (breakfast: 0.4, $p=0.054$; dinner: 0.8, $p=0.0001$; bedtime: 0.6, $p=0.0007$). In terms of perceived metabolic control, the perceived frequency of hyperglycemia decreased significantly at endpoint in the breakfast (–0.4, $p=0.02$) and bedtime groups (–0.5, $p=0.0005$) but not in the dinner group (–0.3, $p=0.07$). Perceived frequency of hypoglycemia decreased significantly in the 3 groups combined (–0.18, $p=0.04$), but not in separate groups. These data complement the clinical study results and, in addition, show treatment satisfaction improved with glargine, regardless of injection time. Thus, insulin glargine can be used effectively according to individual patients' needs or preference, before breakfast, before dinner or at bedtime.

1978-PO

Synthesis and Crystal Structure of a PPARpan Agonist That Delivers Glycemic Control and Improved Lipid Profiles without Weight Gain

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We have previously shown that activation of the PPAR subtypes by simultaneous administration of combinations of selective PPAR agonists produces synergistic effects in ZDF rats (a rodent model of type 2 diabetes, 62nd ADA session abst. # 566 and 567). These effects include normalization of post-prandial glucose and lowering of serum triglycerides and NEFAs without weight gain and less hemodilution. We now show that a single molecule that has agonist activity on PPARα, PPARγ and PPARδ exhibits the same synergy as that reported for the combination of individual selective PPAR agonist molecules. The design, synthesis and in vivo data of such a PPARpan agonist that is a 9nM on PPARγ and 400nM on PPARα and 30nM on PPARδ in the transient transfection assay will be presented. In the ZDF rat model this pan agonist normalized glucose (66% reduction) and lowered triglycerides (79% reduction) without excessive weight gain or hemodilution. Compared with the selective PPARδ agonist GW501516X this molecule contains a piperazine moiety. The x-ray crystal structure of similar compounds complexed with the PPARδ receptor shows that the piperazine occupies a pocket that is conserved in PPARα, PPARδ and PPARγ.

1979-PO

Combination of Repaglinide and Metformin Results in Greater Than Additive (Synergistic) Effects on Glucose Tolerance in Obese Zucker (fa/fa) Rats

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Combination therapy with repaglinide (REP) and metformin (MET) is an effective way to treat patients with type 2 diabetes. In this study, we specifically wanted to investigate whether the combination of REP and MET acutely has additive or possibly synergistic effects on glucose tolerance in male obese Zucker (fa/fa) rats. Twenty overnight fasted Zucker rats were studied in a 2x2 factorial design (n=5 per group). At t=-60 min animals received either MET 200 mg/kg or vehicle (VEH) p.o., at -30 min animals received either REP 0.3 mg/kg or VEH p.o., and at 0 min all animals received 2 g/kg glucose p.o. Tail tip sampling for glucose measurements was performed at -60, -30, 0 (immediately prior to glucose dosing), 30, 60 and 120 min. The area under the glucose curve between 0 and 120 min (AUC_{0-120}) and the glucose value at 120 min (GLU_{120}) were evaluated statistically with two-way analysis of variance. The interaction term was used to test for synergy. Data are presented as mean±SD. As demonstrated in the table, the threshold dose of REP had no effect on either parameter when given alone, but a clear effect when combined with MET dosing. This was evidenced by the interaction terms (significance for GLU_{120}) showing that REP and MET have greater than additive or synergistic effects on glucose tolerance in the male Zucker rat.

	VEH/VEH	REP/VEH	VEH/MET	REP/MET	p value, interaction term
AUC_{0-120} (mMxmin)	947±128	965±166	811±43	614±106	0.061
GLU_{120} (mM)	7.16±0.79	7.02±1.39	6.72±0.23	4.28±0.76	0.011

In conclusion, we have demonstrated that the combination of REP and MET has synergistic effects on glucose tolerance in the male Zucker rat. The presence