OP 32

ADdition of Oral-Lyn™ at Meal-Times in Subjects with Type-2 Diabetes Maintained on Glargine + Metformin - A Comparison with Placebo

Itamar Raz, Angelina Dubinsky, Miriam Kidron, Julio Wainstein

Haddassah Hospital, Jerusalem, Israel

Background and Aims. *The purpose of the study was to determine the metabolic effect of novel oral insulin spray formulation at meal-time, on a long term basis (12 weeks), in subjects with Type-2 diabetes, maintained on once a day s.c. Glargine insulin injection therapy at bed time and Metformin. The primary hypothesis is that Oral-lyn™ can be used safely at meal-times and will improve 7 point glucose profiles, fructosamine and the baseline HbA1c levels 12 weeks after treatment. The Oral-lyn™ system is based on a unique liquid aerosol formulation, which allows a precise insulin dose delivery by mouth.*

Materials and Methods. *This was a randomised, double blind, long term (12 weeks) study in 26 Type-2 diabetic subjects (male or female) with poorly controlled blood glucose maintained on once a day s.c. Glargine + Metformin. After the initial screening visit, subjects maintained their regular treatment for two weeks as a run-in period. Following the training of the Oral-lyn™ device operation and dosing schedules, they were divided into two groups. One group had 7 puffs of Oral-lyn™ TID, and the other group had 7 puffs of placebo TID. Both groups took the puffs 10 min before meal time, in addition to their regular treatment. In cases where self glucose values were above 12mmol/L before any meal or before bedtime, an additional 7 puffs were added. Each subject had routine blood chemistry and HbA1c as well as fructosamine levels at the beginning of the study and at the end of every month during the study period. Beginning with the initial screening visit, each subject had to monitor his/her blood glucose at least three times a day and once a week for a 7-point profile.*

Results. *The interim results, after 8 weeks of treatment, showed no change in fasting glucose while in post-prandial glucose there was a 15.4% reduction (from 211.2mg%+53.7 to 178.5mg%+39.1) in the Oral-lyn™ group versus 3.9% elevation (from 202.7mg%+60.1 to 210.1mg%+5.2) in the placebo group ($p<0.05$). Furthermore, we found a reduction of fructosamine in the Oral-lyn™ group of 6.4% versus 3.6% in the placebo (p-NS) and in HbA1c - 6.6% reduction versus 3.4% in the placebo (p-NS).*

Conclusion. *In Type-2 diabetic patients, maintained on Glargine and Metformin, Oral-lyn™ was especially effective in controlling post-prandial glucose excursions.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 33

A 12-Day Comparison of Preprandial Humulin-R vs Oral-Lyn™ in 10 Type-1 Diabetic Subjects Receiving Baseline Glargine Insulin Therapy

Jaime Guevara-Aguirre, Marco Guevara, Jeannette Saavedra

Institute of Endocrinology IEMYR, Quito-Ecuador, South America

Background and Aims. *The aim of this pilot study was to determine the suitability of dose and formulation of Oral-lyn™ for its use in a larger multi-center trial. We also compared the glucodynamics of both rapid insulins (Oral-lyn™ and Humulin-R) in 10 Type-1 diabetic subjects receiving glargine insulin as their baseline therapy. Fructosamine, a parameter of protein glycation was determined as part of a panel of safety monitoring.*

Materials and Methods. *10 Type-1 Diabetes Mellitus (DM) research subjects received their usual baseline glargine insulin (Lantus) therapy twice daily (BID: 2/3rd in the morning and 1/3rd in the evening). Depending on present glycemia, Humulin-R was dosed as a pre-meal s.c injection during days -3, -2 and -1. Five to eight puffs of Oral-lyn™ were given pre- and post- prandially on days + 1 through + 9. Adjustments of glycemia were done using standard snacks, additional s.c Humulin-R or Oral-lyn™ puffs.*

Results. *Peripheral glucose measurements were self-monitored by the 10 DM Type-1 research subjects in duplicate at each time-point by using a common standard method (Accu-check by Roche). The peripheral glucose concentration average of the 2-value performed at each time-point for the 9-day Oral-LynTM (O), and 3-day Humulin-R (H) are hereby provided: Pre-Breakfast (B): 70.26 (O) vs. 91.08 (H); 1-hour (h) post-B: 138.50 (O) vs. 151.45 (H) ; 2-h post-B: 113.92 (O) vs. 108.18 (H); Pre-Lunch (L): 84.82 (O) vs. 98.55 (H); 1-post-L: 142.00 (O) vs. 140.77 (H); 2-h post-L: 113.55 (O) vs. 106.28 (H); Pre-Dinner (D): 92.84 (O) vs. 100.78 (H); 1-post-D: 141.31 (O) vs. 139.43 (H); 2-h post-D: 119.62 (O) vs. 109.94 (H). The corresponding Area Under the Curve for both treatments were compared and no statistical significance was found (p = 0.6875). Additional data on safety an efficacy, including parameters of protein glycosylation will be presented*

Conclusion. *Using BID glargine insulin (Lantus) as baseline therapy, Humulin-R and Oral-lyn™ induced similar glucodynamic responses during the 12-day observation period. Intensive monitoring and timely corrections with additional snacks, Humulin-R or Oral-LynTM, resulted in an appropriate glycemic control as assessed by individual daily-glycemic curves and, especially, normal preprandial glycemia. Measurements of protein glycosylation displayed a tendency to lower values after the 12-day study period.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 34

Insulin Detemir Reduces Hypoglycaemic Risk at Comparable Hba_{1c} Values Compared to NPH Insulin in Type 1 and Type 2 Diabetes

David Russell-Jones[1], Hansoo Kim[2], Lily Kong[2], Per Clauson[3]

[1] The Royal Surrey County Hospital, Guildford, UK, [2] Novo Nordisk Asia Pacific Pte Ltd, Singapore, [3] Novo Nordisk A/S, Bagsvaerd, Denmark

Background and Aims. *Tight glycaemic control reduces the incidence and progression of long-term diabetic complications but also increases hypoglycaemic risk, thereby limiting the achievable level of glycaemic control through impaired tolerability. Insulin detemir (IDet) is a new basal insulin analogue associated with more predictable glycaemic control and less weight gain compared to NPH insulin in people with type 1 or type 2 diabetes.*

This study investigates whether IDet favourably shifts the relationship between glycaemic control and hypoglycaemic risk at all levels of HbA_{1c} in comparison to NPH insulin. A pooled analysis of 4 multicentre, randomized, clinical trials (16–28 weeks basal-bolus therapy) was made in people with type 1 diabetes. In addition, the same evaluation was made for a trial in type 2 diabetes (24 weeks add-on to oral anti-diabetic [OAD] therapy).

Materials and Methods. *In the pooled analysis of type 1 diabetes, IDet (n=1180) or NPH insulin (n=810) was administered once or twice daily in combination with pre-meal insulin aspart or human soluble insulin. The number of major (blood glucose [BG]<2.8 mmol/l, assistance required) and minor (BG<2.8 mmol/l, no assistance required) hypoglycaemic episodes per person was compared during the last 3 months of treatment in each trial. Analysis of hypoglycaemic risk by HbA_{1c} and hypoglycaemic relative risk (RR) was modelled in a Poisson model with a gamma frailty distribution, using HbA_{1c} as covariate. In the add-on OAD, multicentre, randomized, parallel group clinical trial of 476 insulin-naïve people with type 2 diabetes, a goal-directed titration algorithm was used to achieve good glycaemic control and hypoglycaemic RR was estimated using the same statistical model.*

Results. *From the data of the pooled analysis of type 1 diabetes, baseline demographic and disease status were similar for the two treatment groups. The overall hypoglycaemic RR was 22% lower with IDet than NPH insulin (RR=0.78, p<0.001). At all levels of HbA_{1c}, IDet was associated with a lower hypoglycaemic risk than NPH insulin. Furthermore, the RR reduction increased with lower HbA_{1c}. A similar trend is observed in type 2 diabetes where the overall hypoglycaemic RR was 39% lower with IDet than NPH insulin (RR=0.61, p=0.008), with a risk reduction favouring IDet at all levels of HbA_{1c} and increasing with improving glycaemic control.*

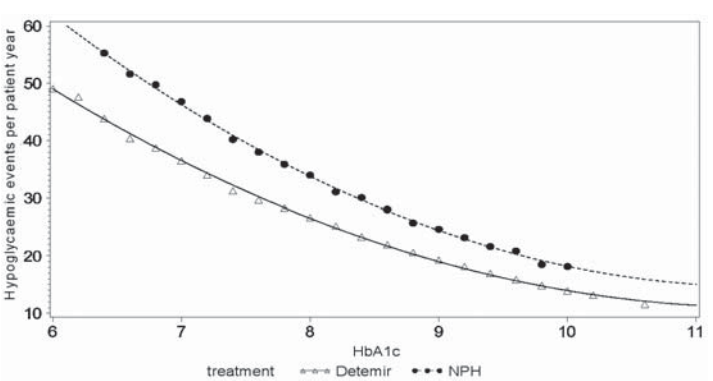


Figure: Hypoglycaemic risk versus HbA_{1c} in type 1 diabetes

Conclusion. *The results suggest that treatment with IDet should enable more people with type 1 or type 2 diabetes to achieve good glycaemic control, with the advantage of a lower associated hypoglycaemic risk when compared to NPH insulin.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 35

The Advantage of Less Weight Gain Increases with BMI When People with Type 2 Diabetes Are Treated with Insulin Detemir Compared to NPH Insulin

Malcolm Nattrass[1], Soren Can Tamer[2], Lily Kong[3], Per Clauson[2]

Selly Oaks Hospital, Birmingham, West Midlands, UK, Novo Nordisk A/S, Bagsvaerd, Denmark
Novo Nordisk Asia Pacific Pte Ltd, Singapore

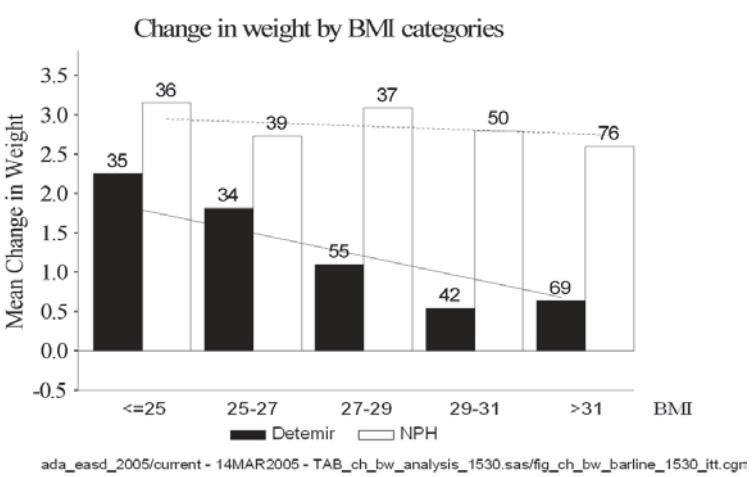
Background and aims. *The initiation or intensification of insulin therapy often results in undesired weight gain, which particularly may be problematic in already overweight people with type 2 diabetes. Insulin detemir (IDet) has not been associated with weight gain (in contrast to NPH insulin) in clinical trials in people with type 1 diabetes, while in people with type 2 diabetes there has been significantly less weight gain associated with IDet compared to NPH insulin. The present analysis aimed to determine whether the extent of this apparent advantage is dependent on the body mass index (BMI) of people with type 2 diabetes at the initiation of treatment with IDet compared to NPH insulin.*

Materials and methods. *Data from a 24 weeks insulin add-on to current oral anti-diabetic (OAD) therapy study in insulin naïve people with type 2 diabetes (n=475) were analysed. People with type 2 diabetes received twice daily IDet or NPH insulin (both in combination with mealtime insulin aspart). Weight change from baseline was analysed using a linear regression model with baseline BMI as covariate.*

A separate analysis exploring the relationship between IDet and NPH insulin in people with high BMI (>35 kg/m2) at baseline was performed on weight change data from two pooled studies in people with type 2 diabetes receiving basal-bolus therapy (n=900).

Results. *Mean HbA1c decreased by 1.84% and 1.90% points with IDet and NPH insulin, respectively, to endpoint values of 6.58% and 6.46% (NS). Regardless of baseline BMI, people with type 2 diabetes gained less weight with IDet than with NPH insulin. With increasing baseline BMI, people gained less weight with IDet (p=0.01). However, this relationship was not found for NPH insulin (NS).*

Figure: Change in weight by BMI categories in type 2 diabetes



A similar pattern in favour of IDet was observed for basal-bolus therapy in people with type 2 diabetes. IDet treated people with high baseline BMI (>35 kg/m2) lost 0.5 kg in average (NS) whereas people with high baseline BMI (>35 kg/m2) receiving NPH insulin significantly gained 2.4 kg in average (p=0.025).
Conclusion. *The discrepancy in weight gain favouring IDet over NPH insulin increases with baseline BMI when these insulins are added to OAD or used in basal-bolus therapy. IDet may therefore offer a weight advantage over NPH insulin, especially in overweight or obese people with type 2 diabetes.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 36

Pharmacokinetics and Pharmacodynamics of Insulin Lispro and Insulin Aspart, and of Insulin Lispro Mixture 25/75 and Aspart 30/70 Pre-Mix in Healthy Subjects Are Comparable

DKW Soon, C Chan, A de la PeÒa,
KP Yeo, LL Teng, JQ Kamerud, M Lim, SD Wise

Lilly-NUS Centre for Clinical Pharmacology, Clinical Research Centre (MD11), National University of Singapore, Singapore

Background and Aims. *Insulin analogues such as insulin lispro (LP) and insulin aspart (AP) have lower self-association and are therefore more rapidly absorbed after subcutaneous (SC) administration than regular human insulin, avoiding the need for a delay between insulin injection and meals. We ran 2 studies comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of LP and AP (Study 1), and of LP mixture 25/75(25% insulin LP/75% insulin LP protamine) and AP 30/70 pre-mix (30% insulin AP/70% insulin AP protamine) (Study 2), after SC administration.*

Materials and Methods. *These were double blind, randomised, crossover studies in non-diabetic subjects. PD was assessed by a manual glucose clamp, where a 20% dextrose solution was infused by a volumetric pump to maintain subjects at euglycaemia. PK was assessed by serial blood sampling up to 8 and 14 hours for studies 1 and 2 respectively. Study 1: (Age: 23+1 yr, BMI: 23+2 kg/m2, n=18 males), each subject received single doses each (0.15 U/kg) of insulin LP and AP on 2 occasions 2 to 21 days apart. Study 2: (Age: 25+5 yr, BMI: 23+2 kg/m2, n=24, 19 males), each subject received single doses (0.25 U/kg) of LP mixture 25/75 and AP 30/70 pre-mix.*

Results. *Selected PK and PD parameters from both studies are presented in table 1. Intra-subject variability assessed using data from the replicate doses administered in Study 1, was 11% for both LP and AP for AUC0-t', and was 20% and 10% for Gtot(Glucose infused) for LP and AP respectively.*

Conclusion. *Insulin LP and AP were similar for their PK and PD profiles, so it does not appear that dose adjustment is necessary if a patient is switched between these insulins. There were no statistically significant differences in the PK profiles of LP mixture 25/75 and AP 30/70 mixture. Although the Gtot and Rmax were*

Table 1. Comparison of PK and PD Parameters (Means(CV%))

	Cmax (pmol)	tmax (min)[(a)]	AUC 0-t' (pmol*min/L)	Maximum Glucose Infusion Rate - Rmax (mg/min)	tRmax (min)	late tRmax 50 (min) Gtot (g)	Glucose Infused -
Lispro	556 (24)	45.0 (30-180)	76300 (22)	431 (19)	102 (51)	227 (22)	75.0 (28)
Aspart	512 (28)	512 (28)	72500 (25)	433 (25)	120 (37)	230 (22)	74.0 (29)
Lispro Low-Mix	305 (26)	60 (30-150)	84600 (28)	266 (53)[(b)]	93.0 (53)	300 (42)	72.0 (68)
Aspart 30/70 Pre-Mix	358 (30)	60 (30-150)	92400 (32)	393 (49)	106 (63)	286 (45)	96.0 (67)

(a) The values are shown as the median with min and max values in ()
(b) Significantly different from aspart 30/70 premix at alpha=0.05

significantly lower by 25% and 32% respectively for LP low-mix, Rmax differences could be explained by the 20% greater rapid acting component in the AP mixture relative to the LP mixture. As insulin treatment generally requires titration in the clinic for individualized therapy, LP and AP mixtures appear to be sufficiently similar in their PD profiles such that switching between them should be safe with the appropriate clinical monitoring.

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 37

Efficacy of Biphasic Insulin Aspart 30 in Patients with Type 2 Diabetes Not Achieving Glycemic Targets on Oads with/without Basal Insulin Therapy

Rajeev Jain, Timothy Wahl, Jack Whalen,
Peter Bressler, Rogelio Braceras, Ling Deng, Alan Garber

Milwaukee Medical Clinic, Milwaukee, WI, USA

Background and Aims. *The objective of this study was to demonstrate that in patients with type 2 diabetes (T2DM) not achieving glycemic targets, the addition of biphasic insulin aspart 30 (30% soluble and 70% protaminated, BIAsp 30, NovoMixÆ 30) can reduce HbA1c levels to d"6.5%.*

Materials and Methods. *This was a three-phase, 48-week, multi-centre, open-label, treat-to-target trial. In Phase 1, patients with T2DM not achieving glycemic targets on oral antidiabetic drugs (OADs), with or without once-daily basal insulin therapy with NPH or glargine, were initiated with 12U BIAsp 30 treatment once-daily before supper, and the dose was titrated based on fasting plasma glucose (FPG) values according to the predefined algorithm below. If HbA1c was > 6.5%, the dosing frequency was increased to twice-daily in Phase 2 by adding 3 or 6 U at breakfast (depending upon FPG) and to thrice-daily in Phase 3 by adding 3 U at lunch, at 16 and 32 weeks, respectively. Dose titration in Phases 2 and 3 was based on the algorithm below. Patients attaining an HbA1c value d"6.5% at the end of any phase were considered to have completed the study.*

Plasma glucose (mmol/L)	<4.4	4.4 to 6.1	6.1 to 7.8	7.83 to 10	>10
Pre-breakfast or supper dose change (U)	-3	No change	+3	+6	+9
Plasma glucose after lunch (mmol/L)		<5.6	5.6 to 7.8	7.83 to 10	>10
Lunchtime dose change (U)		-3	No change	+3	+6

Results. *After Phases 1, 2, and 3, the proportion of patients achieving HbA1c d"6.5% and < 7.0% was 60% and 77%, respectively. Mean daily insulin doses for subjects who achieved an HbA1c d"6.5% at the end of Phases 1, 2, and 3 were 0.6, 0.9, and 1.1 U/kg, respectively. Patients previously treated with OADs and once-daily basal insulin had significant improvements in HbA1c (-0.9%) when switched to once-daily BIAsp 30. The overall rate of major hypoglycaemia was low at 0.14 events per patient/year and there were no incidents of major nocturnal hypoglycaemia. Lipid profile was improved (HDL + 9%, LDL + 0.7%, triglycerides -19%, total cholesterol 4.8%) and blood pressure was reduced (systolic and diastolic -3%).*

Conclusion. *BIAsp30 used once-, twice- or thrice-daily in combination with OAD therapy allows most patients to reach HbA1c targets in T2DM unsuccessfully treated with OADs or basal insulin, with potential beneficial effects on metabolic parameters.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 38

Adding Novomix & Reg; 30 Once or Twice Daily Is More Efficacious Than Optimising Oral Treatment in Patients with Type 2 Diabetes

WB Wan Mohamad, for the BIAsp-3021 Study Group

Hospital Universiti Sains Malaysia, Kelantan, Malaysia

Background and Aims. *The premixed insulin analogue, biphasic insulin aspart 30 (BIAsp30, NovoMix® 30) consists of 30% soluble and 70% protamine-bound insulin aspart. This study was designed to evaluate the efficacy and safety of adding BIAsp30 to existing oral treatments versus optimising oral treatments in patients with type 2 diabetes inadequately controlled with oral monotherapy or combination therapy.*

Materials and Methods. *This 24-week, multi-centre, open-labeled, randomised 2-arm parallel trial was conducted in Australia, Hong Kong, Malaysia, Philippines, Singapore, Taiwan and Thailand. It consisted of a 2-week screening period, followed by 24 weeks of treatment. Subjects randomised to BIAsp30 treatment received BIAsp30 once-daily (o.d.) at dinnertime and those not achieving optimal glycaemic control were switched to twice-daily (b.i.d.) BIAsp30 at midterm. Subjects randomised to OAD-only treatment continued with their previous OAD treatment and the dose was optimised (but the OAD was not changed) in accordance to local practice.*

Results. *A total of 173 subjects completed the trial. A significantly greater reduction in HbA1c from baseline was seen at 11 weeks with BIAsp30 (o.d.) versus OAD-only treatment (1.16±1.01 vs 0.58±0.95% [$p<0.001$]; mean baseline HbA1c: 8.61 and 8.46%, respectively), and this trend continued at 24 weeks, with significantly greater reductions in HbA1c from baseline observed with BIAsp30 (o.d.) and BIAsp30 (b.i.d.) treatments versus the OAD-only treatment (1.24±1.04 vs 1.34±1.33 vs 0.67±1.18%; $p<0.01$). Of the patients in the BIAsp30 (o.d.) group, 46% of patients and an additional 24% from the BIAsp30 (b.i.d.) group achieved the HbA1c target of <7.0%, as compared to 29% of subjects on OAD-only treatment. Consistent with the trends in HbA1c, significantly greater reductions in FPG from baseline was seen at 11 weeks with BIAsp30 (o.d.) versus OAD-only treatment (1.91±2.22 vs 1.01±2.20 mmol/l [$p<0.05$], as well as at 24 weeks, with BIAsp30 (b.i.d.) versus OAD-only treatment (2.32±3.13 vs 1.10±2.37 mmol/l [$p<0.05$]. A total of 178 hypoglycaemic episodes were reported by 69 patients (54%) treated with BIAsp30 and 46 episodes by 19 patients (30%) treated with OAD-only, of which all were minor or symptomatic, except for one in each treatment group which was major. Treatment emergent adverse events (TEAEs) were similar between BIAsp30 and OAD-only treatment. There were 5 serious TEAEs in the BIAsp30 group and none in the OAD-only group. None of these serious TEAEs were likely to be related to the trial product.*

Conclusion. *In type 2 patients not well-controlled with OADs, the addition of NovMix® 30 once or twice daily significantly improves glycaemic control while not posing additional safety concerns to the patients.*

Full text. e-Journal: *http://www.medassocthai.org/journal*

OP 39

Simplified Approach to Insulin Therapy Combining Acarbose as "Regulatory Switch" for Glycemic Control

LK Shankhdhar, K Shankhdhar, U Shankhdhar

L.K.Diabetes Centre, Lucknow, Uttar Pradesh, India

Background and Aims. *A prospective randomized, open label clinical trial Background and aims: Initiating Insulin therapy requires massive information on the part of physicians. In India there are 34 varieties of Insulins with 60 brand names, 2 types of Syringes (U-40, U-100), 3 types of disposal Insulin pens and 3 types of permanent Insulin pens; all with different details as to usage. Approximately 90% diabetic patients consult their family physicians, since Diabetologists are very few and remain either non approachable or non affordable. Driven by ignorance, most family physicians avoid initiating Insulin therapy and even when they dare it, they uses only premix 30/70 Human Insulin and attempt to achieve glycemic control by trying various dose alterations. Under these circumstances there is a need for a simplified method of Insulin therapy. A newer approach to Insulin therapy was discovered by us for secondary OHA failed Type 2 D pts by selecting already adopted premix (30/70) Human Insulin for initiating Insulin therapy with aim to achieve crude control of glycemia; chasing fine control by addition or deletion of different doses of Acarbose.*

Materials and Methods. *Research Design and Methods: In a prospective, randomized, open clinical study of 9 months, 30 pts of secondary OHA failed type 2 Diabetes; were initiated on premix (30/70) Human Insulin as add on therapy to achieve crude glycemic control (empirically defined as fasting around 8mmol/L and post prandial around 14mmol/L) in one month and then randomized into two groups-one attempting to better glycemic control with varying doses of same Insulin (IG) and the other using different doses of Acarbose (AG) with fixed doses of Insulin; both groups having similar characteristics such as age (AG: 58.53±9.14, IG: 59.73±6.39), Sex (AG: 11m/4f, IG: 10m/5f), BMI (AG: 26.4±5.03, IG: 25.4±4.7), duration of diabetes (AG: 12.33±1.79 years, IG: 12.73±1.62 years) and baseline glycemic control (A1c: AG=11.54±0.59, IG= 11.76 ±0.80).*

Results. *AG achieved better A1c reduction of 4.32±0.56 Vs 2.94±0.72 of IG. No pt in IG achieved A1c =7% while 26.6% pts in AG achieved this target. 40% pts in AG did not gain weight compared to only 20% in IG. Weight gain in AG was 0.93±0.96 Kg Vs 1.53±1.18Kg in IG. 2 major hypoglycemic episodes occurred in IG Vs only 1 in AG. 8 episodes of minor hypoglycemia occurred in IG Vs 2 in AG. 20% pts of AG complained of gas with dose relationship, needing no withdrawal or drop out Vs nil in IG.*

Conclusion. *Using premix human Insulin (30/70) in OHA failed type 2 D patients for achieving crude control and finer tuning of glycemia with Acarbose is a newer approach to Insulin therapy, which is more effective, safer and easier than the conventional method, most suited for developing countries. Abbreviations: AG=Insulin+Acarbose group, IG=Only Insulin group, pt=patient, D=Diabetes*

Full text. e-Journal: *http://www.medassocthai.org/journal*