

Evidence Tables

INS 6: Is insulin in combination with oral antidiabetic drugs effective in the control of blood glucose compared to insulin alone in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ, the Metformin Trial Group. Continuing metformin when starting insulin in patients with Type 2 diabetes: a double-blind randomized placebo-controlled trial. <i>Diabetic Medicine</i> 2005; 22(5):634-640. Ref ID: 1154	RCT 1++	N=183	<p>Patients with type 2 diabetes with unsatisfactory glycaemic control on OHA. All but one patient were on maximal doses of oral treatment (n=123 taking at least 2 g of metformin a day). Inclusion criteria: Duration of diabetes of at least 2 years, age 75 yrs or less</p> <p>Exclusion criteria: Intolerant to metformin Due to start nocturnal insulin Breastfeeding/ pregnancy Risk of lactic acidosis Chronic renal failure Cardiac failure</p>	<p>Insulin and metformin No standard protocol for the management for the adjustment of insulin was specified. Target of pre-meal blood glucose 7 mmol/l and HbA_{1c} below 7%. Maximum dose 1g twice a day</p>	<p>Insulin and placebo Insulin protocol as for intervention</p>	12 months	<ul style="list-style-type: none"> • Weight gain • HbA_{1c} • Hypoglycaemic events • Fasting total cholesterol • Triglycerides • Well-being • Treatment satisfaction 	<p>Weight gain The average weight gain over 12 months for the metformin group was 6.1 kg compared with 7.6 kg in the placebo group (adjusted difference (co varying baseline values) 1.5 kg (95% CI 0.2-2.9; P = 0.02). Analysis using repeated measures of weight confirmed this difference (p = 0.009)</p> <p>HbA_{1c} Metformin was associated with a significantly greater reduction in HbA_{1c} compared with the placebo group (1.5% vs 1.3%; adjusted difference 0.5% (0.1-0.9; P = 0.02).</p> <p>Insulin dose At every follow-up visit the metformin group was on a lower total dose of insulin than the placebo group. At 12 months, metformin (62 units) and placebo (86 units) (adjusted difference 25 units (15-34); p < 0.001).</p> <p>Hypoglycaemic events</p>	United Bristol Hospitals and NHS Executive Southwess t

			<p>Pulmonary disease Liver disease Alcohol dependence. The study population (means) was:</p> <ul style="list-style-type: none"> • age 58 yrs 65% male. • duration of diabetes 9.5 yrs mean BMI 31.2 kg/m². • HbA_{1c} values 9.9% • total cholesterol 5.1 mmol/l • HDL cholesterol 1.1 mmol/l • triglycerides 2.7 mmol/l 					<p>Individuals in the metformin group were more likely to experience hypoglycaemic events than those in placebo. At least one episode of hypoglycaemia during the 12 months was reported by 63/77 patients (82%) in the metformin group and 48/73 (66%) patients in the placebo group (relative risk 1.24 (1.02-1.51), p = 0.027). Severe hypoglycaemia was reported by 10 patients (13%) taking metformin and one patient (1%) taking placebo (RR 9.48 (1.24-72.2), p = 0.009)</p> <p>Total cholesterol, HDL cholesterol and triglycerides No change in either group over the course of the trial</p> <p>Self reported outcome measures There was a greater improvement in diabetes treatment satisfaction in the metformin group than placebo group (p < 0.001). Changes between baseline and 12 months in 'positive well being' and 'anxiety' were significantly greater in the metformin group (p = 0.02 and p = 0.04 respectively)</p>	
Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus	Cochrane systematic review 1++	N=1811 20 RCTs (28 comparisons)	Patients with type 2 diabetes mellitus (according to appropriate diagnostic criteria	Insulin monotherapy	Combinations of insulin with single or multiple oral hypoglycaemic	Weighted mean trial duration was 10 months	<ul style="list-style-type: none"> • Any diabetes related morbidity • Glycaemic control (fasting 	Insulin monotherapy vs combinations of insulin with single or multiple oral hypoglycaemic agents (OHA) (28 comparisons) (N=20	None

<p>combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2004;(4):CD003418. Ref ID: 1135</p>		<p>(search until March 2004)</p>	<p>of the time) and inadequate glycaemic control despite oral hypoglycaemic agents</p>		<p>agents</p>	<p>(range 2 to 36 months)</p>	<p>blood glucose, HbA1, HbA_{1c}).</p> <ul style="list-style-type: none"> • Quality of life • Patient satisfaction • Amount of insulin necessary for good glycaemic control. • Adverse effects (incidence of hypoglycaemia , weight gain, gastrointestinal symptoms). 	<p>studies)</p> <p>Diabetes-related morbidity, mortality and total mortality</p> <ul style="list-style-type: none"> • No studies assessed these outcomes <p>Glycaemic control</p> <p>(a) <i>Once daily insulin monotherapy regimens (9 comparisons)</i></p> <ul style="list-style-type: none"> • Data from 5 five comparisons comparing a single evening insulin to evening insulin combined with a sulphonylurea (SU) were pooled in a meta-analysis. Insulin-OHA combination therapy was associated with a significant mean (pooled weighted mean difference) lowering of HbA_{1c} of 0.3% (95% CI 0.0 to 0.6; p=0.03) compared to insulin monotherapy (a single evening insulin injection). <p>(b) <i>Twice daily insulin monotherapy regimens</i></p> <p>(i) Bedtime neutral protamine Hagedorn (NPH) insulin plus OHA:</p> <ul style="list-style-type: none"> • Bedtime NPH plus SU (3 comparisons) No significant differences reported • Bedtime NPH plus metformin (1 comparison) 	
---	--	----------------------------------	--	--	---------------	-------------------------------	---	--	--

								<p>Insulin-OHA combination therapy was associated with a significant lowering of HbA_{1c} of 0.6% (P < 0.05) compared to insulin monotherapy</p> <ul style="list-style-type: none"> -Bedtime NPH plus SU plus metformin (3 comparisons) No significant differences reported <p>(ii) Morning NPH insulin plus OHA:</p> <ul style="list-style-type: none"> Twice-daily insulin monotherapy compared with morning NPH insulin combined with SU (3 comparisons) or SU plus metformin (1 comparison): Insulin monotherapy was associated with a significant mean (pooled weighted mean difference) lowering of HbA_{1c} of 0.4% (95% CI 0.1 to 0.8; p = 0.03) compared to insulin-OHA combination therapy. <p>(iii) Twice-daily insulin plus OHA:</p> <ul style="list-style-type: none"> Insulin monotherapy compared with twice-daily (morning and bedtime) premixed insulin (30/70) combined with SU (3 comparisons) One trial reported a significant lower HbA_{1c} for combination therapy (P < 0.05) <p>(c) <i>Multiple daily insulin injections</i> (3 comparisons)</p>	
--	--	--	--	--	--	--	--	---	--

								<ul style="list-style-type: none">• No significant differences reported <p>Hypoglycaemia Heterogeneity in the definitions used and the quality of reporting of hypoglycaemia precluded the pooling of data.</p> <ul style="list-style-type: none">• Of the 14 studies (22 comparisons) that reported hypoglycaemia, in all but one comparison, no significant difference in the frequency of hypoglycaemic events between insulin monotherapy and insulin-OHA combination therapy was demonstrated. Overall, only one episode of severe hypoglycaemia was reported <p>Insulin dose</p> <ul style="list-style-type: none">• Overall, insulin OHA combination therapy was associated with a weighted mean relative reduction in total daily insulin requirement of 46% (range -5 to 74%) compared to insulin monotherapy.• Compared with a single daily insulin injection, regimens combining a SU with a matched daily insulin injection were associated with a 29% relative	
--	--	--	--	--	--	--	--	--	--

								<p>reduction in total daily insulin dose.</p> <ul style="list-style-type: none">• Compared with twice daily insulin, combination regimens with bedtime NPH insulin were associated with relative reductions of 57%, 29% and 64% for SU, metformin or both oral agents, respectively. <p>Well being, quality of life and treatment satisfaction</p> <ul style="list-style-type: none">• Chow 1995 found similar significant improvements in subjective well-being following the initiation of insulin therapy in both groups. However significantly more patients in the combination therapy group wanted to continue insulin therapy at the end of the study (89% vs. 76% for insulin monotherapy, $p < 0.0001$).• Yki-Jarvinen 1992 found insulin therapy with all insulin treatment regimens was associated with significantly greater improvement in the subjective sense of well-being (74%, 84%, 100% and 86% for the multiple insulin injection, OHA plus morning NPH, OHA and evening NPH and twice	
--	--	--	--	--	--	--	--	--	--

								<p>daily insulin mixture groups respectively) compared to the control group (41% improvement) (P<0.001).</p> <p>Adverse effects <i>Weight gain</i> (n=15) Only the results of studies in three subgroups were pooled statistically (a) <i>Once-daily insulin monotherapy regimens</i></p> <ul style="list-style-type: none"> • One cross-over study reported significantly greater weight gain for patients when treated with insulin OHA combination therapy mean 2.6 ± 1.8kg) compared to insulin alone (0.6 ± 2.2kg, p<0.01) though a significant confounding carry-over effect was observed. <p>(b) <i>Twice-daily insulin monotherapy regimens</i> (i) Bedtime NPH insulin plus OHA</p> <ul style="list-style-type: none"> • Bedtime NPH plus SU (3 comparisons) No significant differences reported • Bedtime NPH plus metformin (1 comparison) Insulin-OHA combination therapy resulted in a significant mean 3.7 kg less weight gain compared to insulin monotherapy (P < 0.01) 	
--	--	--	--	--	--	--	--	--	--

								<ul style="list-style-type: none"> • Bedtime NPH plus SU and metformin (3 comparisons) No significant differences reported (ii) Morning NPH insulin plus OHA <ul style="list-style-type: none"> • No significant differences reported (iii) Twice-daily insulin plus oral hypoglycaemic agents <ul style="list-style-type: none"> • No significant difference between insulin OHA combination therapy compared to insulin monotherapy (c) <i>Multiple-daily insulin injections</i> <ul style="list-style-type: none"> • Compared with insulin monotherapy, insulin OHA combination therapy (two studies) was associated with a significant (pooled weighted mean difference with two comparisons) 1.1 kg less weight gain (95%CI:0.5 to 1.7; p<0.001) 	
Goudswaard AN, Stolk RP, Zuihthoff P, de Valk HW, Rutten GE. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. Journal of Family Practice 2004; 53(5):393-399.	RCT 1++	N=69	Patients with type 2 diabetes not controlled with oral hypoglycaemic (OHA) agents alone Inclusion criteria: Younger than 76 years, had HbA _{1c} ≥7.0% despite treatment with both sulfonylurea (SU)	N=33 Insulin combination therapy (IC). NPH insulin at bedtime in addition to current treatment with SU and metformin. Insulin therapy was initiated with	N=31 insulin monotherapy (IM). 30% soluble and 70% NPH insulin therapy initiated with 12 and 6 IU before breakfast and dinner. Protocol as for	12 months	<ul style="list-style-type: none"> • HbA_{1c} measured by turbidimetric inhibition immunoassay (normal range 4-6%) • Body weight • Frequency and severity of hypoglycaemic symptoms 	Glycemic control and insulin dose <ul style="list-style-type: none"> • Adjusted for baseline values, HbA_{1c} for IM fell by 0.14% more than for IC (p=NS). In the IC group, 36% of patients reached HbA_{1c} levels <7.0% compared with 42% in the IM group (P = NS). • When treatment failures 	None

Ref ID: 78			<p>and metformin, willing to start insulin therapy and deemed by their family physician to be candidates for more tight glycemic control.</p> <p>The study population(means) was:</p> <ul style="list-style-type: none"> • 48% male, • age 58.5 yrs, • body weight* 96.3 (IC) vs 81.0 (IM) kg, • BMI* 33.2 kg/m² (IC) vs 28.5 kg/m² (IM), • HbA_{1c} 8.6% <p>* denotes significant difference</p>	<p>8 IU before bedtime. Insulin doses were adjusted twice weekly by telephone contact with the diabetes nurse (adjusting phase), aiming for a target fasting blood glucose of 4.0-7.0 mmol/L and a target postprandial glucose of 4.0-20.0 mmol/L. When targets were achieved and stable, insulin dose was fixed and telephone contacts were decreased to once monthly (stable phase)</p>	intervention		<ul style="list-style-type: none"> • Hypoglycaemic symptoms checklist (range 0-108) • Diabetes Treatment Satisfaction Questionnaire (DTSQ) (range 0-36) • Well Being Questionnaire (WBQ-12) (range 0-36) • Fear of self-injecting with insulin (FSI), Diabetes Fear of Injecting and Self-Testing Questionnaire (D-FISQ) 	<p>(see below) were omitted, mean decrease of HbA_{1c} for IC was 1.0 ± 1.2%. Mean daily insulin dosages at endpoint were 25.8 ± 12.2 IU for IC vs 68.3 ± 27.5 for IM. Mean daily dosages adjusted for body weight were 0.27 ± 0.13 IU/kg for IC vs 0.86 ± 0.37 for IM</p> <p>Treatment failures</p> <ul style="list-style-type: none"> • In the IC group 8 patients (24%) failed to reach glucose targets with a daily dose of 40 IU NPH insulin. Mean daily insulin dosages at endpoint, adjusted for body weight, were 0.41 ± 0.13 IU/kg for treatment failures vs 0.23 ± 0.11 for non-treatment failures (95% CI 0.10 to 0.28; P<0.001). In the IM group 2 patients (65) were switched to another insulin regimen due to unsatisfactory diurnal glucose profiles <p>Weight gain</p> <ul style="list-style-type: none"> • Adjusted for baseline values, body weight in the IM group increased by more than 3.0 kg more than in the IC group (95% CI, 0.68 to 5.25; P=0.01) <p>Hypoglycaemic events and symptoms</p> <ul style="list-style-type: none"> • The average number of hypoglycaemic events per 	
------------	--	--	--	---	--------------	--	--	---	--

								<p>patient was 2.7 ± 5.2 in the IC group, and 4.3 ± 4.3 in the IM group ($P=0.02$). For the number of events accompanied by documented blood glucose levels the difference was not significant. All except one event were mild. The difference between the groups on hypoglycaemic symptom scores was not significant.</p> <p>Diabetes treatment satisfaction and general well-being</p> <ul style="list-style-type: none"> Satisfaction with treatment, adjusted for baseline values, improved in both groups but there was no significant difference between them. Well-being scores, increased from 21.7 ± 8.1 to 25.1 ± 6.8 in the IC group, vs 22.7 ± 6.9 to 22.8 ± 7.6 in the IM group. Adjusted for baseline values, well-being for IC improved by 3.0 points more than IM (95% CI, 0.02 to 5.8; $P=0.05$) <p>Fear of self-injecting and self-testing</p> <ul style="list-style-type: none"> Approximately 70% of patients in both groups had scores of 0 (no fear at all) on both scales. There were no significant differences between the groups on
--	--	--	--	--	--	--	--	---

								either scale.	
Raz I, Stranks S, Filipczak R, Joshi P, Lertoft B, Rastam J et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. Clinical Therapeutics 2005; 27(9):1432-1443. Ref ID: 586	RCT 1++	N=283 (27 sites in 8 countries)	Patients with type 2 diabetes Inclusion criteria: Treatment with SU therapy ≥ 3 months before screening and insufficient glycaemic control (HbA _{1c} 7.4%-14.7%) Whether the patients were previously on a maximum or stable dose of SU was not assured Age ≥ 18 yrs BMI ≤ 40 kg/m ² Exclusion criteria Patients with a significant disease or condition likely to effect trial or health outcomes The study population (means) was: age 55.9 yrs BMI 29.5 kg/m ² , duration of diabetes 9.7 yrs HbA _{1c} 9.5%.	N=93 BIAsp 30 plus pioglitazone (PIO) BIAsp 30 twice daily with and PIO mg once daily. The BIAsp dose was titrated individually to achieve target blood glucose levels of 5 to 8 mmol/L (90-144 mg/dL) for fasting, preprandial and nighttime measurements, and 5 to 10 mmol/L (90-180 mg/dL) for postprandial readings	N=91 Glibenclamide (GLIB) plus PIO GLIB up to 15 mg daily (some patients exceeded this dose). PIO as for intervention N=97 BIAsp 30 As for intervention	18 weeks	<ul style="list-style-type: none"> HbA_{1c} 7- and 8-point blood glucose profiles. Target for fasting, preprandial and nighttime blood glucose was 90 to 144 mg/dL and for postprandial blood glucose 90 to 180 mg/dL. cardiovascular risk factors 	<p>Insulin dose The increase in mean BIAsp dose from the beginning to the end of the trial was significantly larger in the monotherapy group than the BIAsp30 plus PIO group (0.40 U/kg vs 0.30 U/kg; p = 0.002).</p> <p>HbA_{1c} After the 18-week treatment period, HbA_{1c} levels in the BIAsp 30 plus PIO group were significantly lower than in the GLIB plus PIO group (mean [SD], -0.64%[0.23%]; p = 0.005) and the BIAsp 30 monotherapy group (-0.60%[0.22%]; p = 0.008). Mean (SD) end-of-trial HbA_{1c} values were 8.4% (1.2%) for the BIAsp 30 monotherapy group, and 9.0% (2.1%) for the GLIB plus PIO group. From baseline to end of trial, HbA_{1c} values decreased in all three treatment groups but the reductions were not significant</p> <p>Fasting blood glucose (FBG) FBG levels were statistically lower in the BIAsp 30 plus PIO group compared with GLIB plus PIO group (153[45] mg/dL vs 169[65] mg/dL, respectively; p = 0.012). The reductions seen in FBG at the end of trial compared with baseline were not significant.</p> <p>8-point blood glucose profile</p>	Novo Nordisk A/S

								<p>By the end of the trial, each time point on the 8-point blood glucose profile was significantly in patients who received BIAsp 30 plus PIO compared with those who received GLIB plus PIO lower ($p < 0.001$ to $p < 0.05$). Measurements taken before dinner, 90 minutes after dinner, and at bedtime were lower for the BIAsp 30 plus PIO group than the BIAsp 30 monotherapy group ($p < 0.05$). The mean (SD) blood glucose level (from 8-point end-of-trial blood glucose readings) was significantly lower for patients treated with BIAsp 30 monotherapy (178[41] mg/dL) or BIAsp 30 plus PIO (164[34] mg/dL) than for those treated with GLIB plus PIO (196[70] mg/dL; $p < 0.01$ vs BIAsp 30 monotherapy and $p < 0.001$ vs BIAsp 30 plus PIO).</p> <p>Prandial blood glucose increment</p> <p>At the end of trial, the mean prandial increment (postprandial glucose minus preprandial glucose) after breakfast, lunch, and dinner for BIAsp 30 plus PIO was significantly lower than seen for GLIB plus PIO (-14 mg/dL; $p = 0.012$). In addition, blood glucose excursion following breakfast was significantly lower for both the BIAsp 30 plus PIO group and</p>	
--	--	--	--	--	--	--	--	---	--

								<p>the BIAsp 30 monotherapy group than the GLIM plus PIO group (28 ng/dL [p = 0.003] and 21 mg/dL [p = 0.025], respectively). There were no other significant between-group differences in prandial increment at any of the other meals.</p> <p>Cardiovascular risk factors</p> <p>Mean (SD) end-of-trial triglyceride levels were significantly lower in the BIAsp 30 monotherapy (158 [88] mg/dL) and BIAsp plus PIO (149 [88] mg/dL) groups than in the GLIM plus PIO groups (211 [211] mg/dL). Triglyceride values in patients who received BIAsp 30 monotherapy were 30 mg/dL lower than those who received GLIB (p < 0.05), while those receiving BIAsp 30 plus PIO showed a 39 mg/dL difference compared with the GLIB plus PIO (p < 0.01). Triglyceride levels in all treatment groups remained within the reference range (0-202 mg/dL for men and women) during the trial period, with the exception of the GLIB plus PIO group at the end of the trial. There were no between treatment differences in end-of-trial vs baseline total cholesterol. At end-of-trial HDL cholesterol levels were significantly higher in the groups</p>	
--	--	--	--	--	--	--	--	---	--

								<p>receiving BIAsp 30 plus PIO than in the other two groups (mean [SD], 4 [1] mg/dl via BIAsp 30 monotherapy [P ≤ 0.001]; 3 [1] mg/dL vs GLIM plus PIO [P < 0.01]). There were no significant differences between the groups in LDL cholesterol. In a subset of the population, PAI-1 values decreased in all groups, most markedly in the BIAsp 30 plus PIO group (from 5.5 to 3.1 ng/dL). PAI-1 was significantly lower with BIAsp 30 plus PIO than with GLIM plus PIO at the end of the trial (mean [SD], -1.9 [0.6] ng/dL; p = 0.001)</p> <p>Adverse events (AEs)</p> <p>The most commonly reported AEs (incidence >5%) were upper respiratory tract infections (13%-21% of exposed patients), headaches (4%-10%), edema (12%-9%), and weight increase (2%-8%). More patients experienced product-related AEs in the BIAsp 30 plus PIO group (28%) compared with patients received BIAsp monotherapy (20%) or GLIM plus PIO (16%). BIAsp 30 plus PIO was associated with a higher proportion of patients experiencing peripheral edema (6%) compared with GLIM plus PIO (1%) and BIAsp 30 (0%). More patients in the BIAsp 30 plus PIO experienced an</p>	
--	--	--	--	--	--	--	--	--	--

								<p>increase in weight (8%; mean weight gain 4.0 kg) compared with those in the BIAsp monotherapy group (3%; mean weight gain, 2.2 kg) and the GLIM plus PIO group (2%; mean weight, 2.2 kg). There were two serious AEs (cellulitis and myocardial infarction) but these were not thought to be product-related. There were no major hypoglycaemic events. Fewer minor hypoglycaemic episodes were experienced in the GLIM plus PIO group (3 episodes) versus the BIAsp 30 plus PIO group (15 episodes) and the BIAsp 30 monotherapy group (47 episodes). The incidence of all hypoglycaemic episodes was significantly higher in the BIAsp 30 monotherapy group than in the other treatment groups: 0.312 event per patient-week for BIAsp 30 versus 0.083 event per patient-week for BIAsp 30 plus PIO (BIAsp 30 plus PIO/BIAsp 30 ratio of incidence rates with 95% CI, 0.64[0.51-0.80]), and 0.032 event per patient-week for GLIM plus PIO (GLIM plus PIO/BIAsp 30 ratio of incidence rates with 95% CI, 0.27 [0.20-0.37]). The rate of hypoglycaemia was significantly higher for BIAsp 30 plus PIO</p>	
--	--	--	--	--	--	--	--	---	--

								than for GLIM plus PIO (BIAsp 30 plus PIO/GLIM plus PIO ratio of incidence rates with 95% CI, 2.36[1.68-3.31]). There were 8 episodes of nocturnal hypoglycaemia in patients receiving BIAsp 30 monotherapy	
Janka HU, Plewe G, Riddle MC, Kliebe FC, Schweitzer MA, Yki JH. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes.[see comment]. Diabetes Care 2005; 28(2):254-259. Ref ID: 80	RCT 1+ (66 sites in 10 European countries).	N=371 type 2 insulin naïve patients	Inclusion criteria: Male or female patients aged 35 to 75 years with a type 2 diabetes duration of at least 1 year and treated with sulfonylurea and metformin for at least a month. BMI had to be less than or equal for 35 kg/m ² , HbA _{1c} levels between 7.5 and 10.5% and FBG levels greater than or equal to 120 mg/dl. The study population was 59% male, with mean age 60 years, mean weight 85kg, mean BMI 30 kg/m ² , mean HbA _{1c} of 8.8%, mean FBG 171 mg/dl (9.5 mmol/l).	N=177 Glargine plus OAD group: Insulin glargine given once daily in the morning (starting dose 10 IU) plus oral antidiabetic drugs (3 or 4mg glimepiride plus metformin at the same dose as before study entry). Insulin doses were adjusted by a forced titration regimen calling for weekly adjustments for 8 weeks at 2 weekly intervals. The FBG target was 100 mg/dl and the before dinner blood glucose target for the 70/30 group was 100 mg/dl with a step-wise	N=187 70/30 group: Human remixed insulin (30% regular, 70% NPH insulin) administered twice daily before breakfast (starting dose 10IU) and dinner (starting dose 10IU) while glimepiride and metformin were discontinued. Insulin protocol as for intervention	24 weeks	<ul style="list-style-type: none"> • Glycaemic control • Insulin dose • Hypoglycaemia • Weight gain • Adverse events 	Mean HbA _{1c} decrease from baseline was significantly more pronounced (-1.64 vs. -1.31%, p=0.0003) with glargine plus OAD than with 70/30. An HbA _{1c} level of less than or equal to 7% was achieved by 49.4% of patients in the glargine plus OAD group compared with 39% in the 70/30 group (p=0.0596). Significantly more patients on glargine plus OAD (45.5% than on 70/30 (28.6%) reached an HbA _{1c} of less than or equal to 7% without an episode of confirmed nocturnal hypoglycaemia (p=0.0013). FBG decrease was greater with glargine plus OAD (adjusted mean difference -17mg/dl (-0.9 mmol/l) p<0.0001), and more patients reached target FBG of less than or equal to 100 mg/dl with glargine plus OAD than with 70/30 (31.6 vs 15.0%, p=0.0001). Patients received more than twice as much daily insulin with 70/30 than with glargine plus OAD (64.5 vs. 28.2 IU). 61.6% of those receiving	Supported by Aventis Pharma

				increase of insulin depending on blood glucose values.				glargine plus OAD and 67.2% of those receiving 70/30 experienced at least one hypoglycaemic event (p=0.2838). During treatment the rate of confirmed hypoglycaemic events expressed as episodes per patient years was significantly lower with glargine plus OAD for all hypoglycaemic events (4.07 vs 9.87, <0.0001) symptomatic events (2.62 vs 5.73, <0.0009) and nocturnal events(0.51 vs 1.04, <0.0449) . Severe hypoglycaemia was very uncommon in both groups. Mean weight gain did not significantly differ between the two groups (1.4 ± 3.3 vs 2.1 ± 4.2 kg, p=0.0805). The incidence of adverse events was similar with 50.3% in the glargine plus OAD group and 48.7% in the 70/30 group experiencing at least one adverse event.
Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes, Obesity & Metabolism 2006; 8(1):39-48. Ref ID: 3132	RCT 1+	N=341 randomised , patients from 11 countries in Europe.	Inclusion criteria: patients with Type 2 diabetes. All patients had been receiving at least 850mg metformin/day for at least 1 month. Mean age 55 yrs in the BIAsp group, 56	N=111 allocated (N=107 exposed) BIAsp 30, initial daily dose 0.3 U/kg body weight/day Doses of BIAsp 30 and	N=116 allocated (N=108 exposed), BIAsp + metformin 0.2 U/kg body weight/day N=114 allocated	16 weeks	Mean HbA _{1c} ; lipid profile (TG, HDL cholesterol levels); mean post -prandial glucose (based on average blood glucose after 3 meals/day); mean body weight and adverse events (AEs).	Patients in the BIAsp 30 + metformin group had significantly lower mean HbA _{1c} than those treated with BIAsp 30 alone (0.39%, p=0.007), but was not significantly different from glibenclamide + metformin (0.20%). There was no significant difference between the

			<p>58 yrs in the BIAsp + metformin and 47% were male in the groups respectively. Mean BMI was 30.9, 30.4 and 30.5 kg/m² respectively and mean HbA1c was 9.6%, 9.3% and 9.4% respectively.</p>	<p>glibenclamide were gradually increased during the trial. Mean doses for BIAsp 30 were increased from 0.3 rising to 0.51 U/kg/day in the monotherapy group compared to 0.2 rising to 0.30 in the BIAsp 30 + metformin group. Mean starting dose of glibenclamide was 2.33 rising to 6.58 mg by the end of the trial. Dose of metformin remained unchanged throughout the trial (approx. 1660 mg/day) and was similar between the two groups receiving it.</p>	<p>(N=114 exposed), Metformin + Glibenclamide (1.75mg once daily gradually increased every 3-7 days in 1.75mg increments up to maximum 10.5mg daily dose).</p>			<p>treatment groups for mean post-prandial blood glucose and for before-breakfast glucose.</p> <p>Body weight increased for all 3 treatment groups by the end of the study (1.6kg, 0.8 kg and 0.1 kg for BIAsp 30, BIAsp + metformin and Metformin + Glibenclamide groups respectively). There was no significant difference in end-of trial body weight between the BIAsp 30 + metformin compared to the glibenclamide + metformin group (-0.66 kg difference) and between BIAsp 30 + metformin compared to BIAsp 30 alone (-0.80 kg difference).</p> <p>However, end-of trial body weight was significantly higher for the BIAsp 30 group compared to the glibenclamide + metformin group (-1.46 kg difference).</p> <p>There was no significant difference in triglyceride (TG) reduction or HDL-cholesterol increase, between the three treatment groups.</p> <p>The proportions of patients who had at least one adverse event were: 42%, 31% and 24% in the BIAsp 30, BIAsp + metformin and Metformin + Glibenclamide</p>
--	--	--	--	---	--	--	--	---

								groups respectively. 95% of the events were deemed to be unrelated to the trial.	
Stehouwer MHA, DeVries JH, Lumeij JAE, Ader HJ, Engbers et al. Combined bedtime insulin – daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA _{1c} and hypoglycaemia rate – a randomised trial. Diabetes Metabolism Research and Reviews 2003; 19: 148-152 Ref ID: 3131	RCT 1+	N=261	Obese type 2 diabetic patients with secondary failure to oral blood-glucose lowering agents (sulphonylurea (SU) plus metformin) Inclusion criteria: HbA _{1c} > 7.0% with diet and oral hypoglycaemic drugs (at least 3 tablets of SU and 1g metformin) age 40 to 70 years BMI 25-40 kg/m ² 12-week run phase: glimepiride (GLIM) and metformin (500 mg twice daily). GLIM was titrated up to 6 mg, targeting a fasting blood glucose (FBG) below 7.4 mmol/L. Patients with a HbA _{1c} > 6.5% were randomly assigned to the treatment or control groups	N= 86 GLIM plus NPH insulin at bedtime. In all groups, the metformin was stopped. During the 9-month treatment phase, the glycaemic targets were 4.0 to 7.4 mmol/L for FBG levels and 4.0 to 10.0 mmol/L for postprandial levels. The therapeutic aim was HbA _{1c} level ≤ 6.5%	N=88 NPH insulin twice daily N=87 Mixture of short- and intermediate-acting insulin twice daily. Target levels as for intervention	9 months	<ul style="list-style-type: none"> • HbA_{1c} • Hypoglycaemic events • body weight • BMI kg/m² • daily insulin dose • home blood-glucose measurements 	<p>HbA_{1c} The mean (SD) HbA_{1c} (%) was significantly higher in the GLIM plus NPH insulin group as compared to the NPH and mixed insulin groups (8.9 (1.2) vs 8.3 (1.0) and 8.3 (1.2), respectively, p < 0.001). The target HbA_{1c} was reached in a small minority of patients only, 1.2%, 3.4 and 5.7% in GLIM plus NPH, NPH insulin vs mixed insulin, respectively,</p> <p>Hypoglycaemic events The incidence of hypoglycaemic events and the number of patients experiencing such an event were similar in all treatment groups. No serious hypoglycaemic events, requiring the assistance of another person, occurred during the study, in any of the groups.</p> <p>Body weight The mean weight gain was comparable in the three groups</p> <p>Insulin dose The mean insulin dose was not statistically significantly different between the groups</p>	Aventis
Altuntas Y, Ozen B, Ozturk B, Sengul A,	RCT 1-	N=60	Patients with secondary oral anti-diabetic drug failure	N=20 Lispro insulin plus metformin	N=20 Lispro insulin plus NPH insulin	6 months	<ul style="list-style-type: none"> • 10-point blood glucose profile 	<p>Home blood glucose monitoring The morning fasting blood</p>	None stated

<p>Ucak S, Ersoy O et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. Diabetes, Obesity & Metabolism 2003; 5(6):371-378. Ref ID: 105</p>			<p>(defined as initial stabilisation on blood glucose (BG) control for a minimum of 6 mths, followed by a lack of control using maximal dose of a sulphonylurea (SU) and despite full compliance with diet). The study population (means):</p> <ul style="list-style-type: none"> • age 54.4 yrs • BMI 31.4 kg/m² • duration of diabetes 7.2 yrs • C-Peptide 1.2 nmol/l • C-Peptide (6 min) 1.9 nmol/l • HbA_{1c} 9.7% 	<p>Initial recommended dose of Lispro insulin 0.3 U/kg/day 850 mg of metformin twice daily (morning and dinner) The target level for the 2 hr post-grandial glucose levels was 8.9 mmol/l</p>	<p>Lispro insulin as for Intervention. 0.2 U/kg of NPH insulin was administered subcutaneously at bedtime only</p> <p>N=20 Regular insulin plus NPH insulin Initial recommended dose of regular insulin 0.3 U/kg/day administered subcutaneously in divided doses pre-meal. Injected 30-45 min before meal. NPH insulin as above.</p>		<ul style="list-style-type: none"> • Serum HbA_{1c} • Basal and stimulated C-peptide levels • Serum HbA_{1c} total cholesterol • Triglyceride • High-density lipoprotein (HDL) • Low-density lipoprotein LDL • Cholesterol • BMI 	<p>glucose (FBG) values were significantly lower in the lispro plus NPH group compared with lispro plus metformin and regular insulin plus NPH group (8.51 ± 2.71, 9.23 ± 2.06 and 9.24 ± 3.13 mmol/l, respectively, p = 0.041). FBG values were not significantly different between the last two groups. 1 hr morning post-prandial glucose values were significantly lower in the lispro plus NPH group when compared with lispro plus metformin (p = 0.02) and regular insulin plus NPH groups (p < 0.001) (9.26 ± 3.12, 10.17 ± 2.86 and 11.10 ± 3.32 mmol/l respectively). Between lispro plus metformin and regular insulin plus NPH groups, there was a significant difference (p = 0.025)</p> <p>2 hour morning post-grandial glucose values were significantly lower both in the lispro plus NPH and in the lispro plus metformin groups when compared with regular insulin plus NPH group (7.91 ± 3.12, 8.05 ± 2.74 and 10.63 ± 3.32 mmol/l, respectively, p < 0.0001)</p> <p>The pre-lunch glucose values were significantly lower in the lispro plus metformin group when compared with both lispro plus NPH (p = 0.015) and</p>	
---	--	--	---	---	--	--	--	--	--

								<p>regular insulin plus NPH groups ($p < 0.001$) (7.53 ± 2.42, 8.59 ± 3.72 and 9.38 ± 3.72 mg/dl respectively). There was a significant difference between lispro plus NPH and regular insulin plus NPH groups ($p = 0.028$). Lunch 1 hr post-prandial glucose values were significantly lower in the lispro plus metformin group when compared with both lispro plus NPH ($p = 0.001$) and regular insulin plus NPH groups ($p < 0.001$) (8.34 ± 2.29, 9.93 ± 4.03 and 10.73 ± 3.56 mmol/l respectively). There was a significant difference between lispro plus metformin and regular insulin plus NPH groups ($p < 0.001$).</p> <p>Lunch 2 hr post-prandial glucose values were lower in the lispro plus metformin when compared with lispro plus NPH (8.19 ± 2.57 vs 8.86 ± 3.57 mg/dl, $p > 0.05$). Lunch 2 hr post prandial glucose values were significantly lower in the lispro plus NPH group when compared with regular insulin plus NPH group (8.86 ± 3.57 vs 10.66 ± 4.36 mg/dl, $p < 0.001$).</p> <p>Lunch 2 hr post-prandial glucose values were significantly lower in the lispro plus metformin group when compared with regular insulin plus NPH group (8.19 ± 2.57 vs</p>	
--	--	--	--	--	--	--	--	--	--

								<p>10.66 ± 4.36 mmol/l, p < 0.001). The pre-dinner glucose levels were similar both in the lispro plus metformin and in the lispro plus NPH groups but were significantly lower as compared with regular insulin plus NPH group (8.99 ± 2.7, 9.0 ± 3.6 and 11.06 ± 4.27 mmol/l respectively)</p> <p>Dinner 1 hr post-prandial glucose values were similar in both in the lispro plus metformin and in the lispro plus NPH groups but were significantly lower compared with regular insulin plus NPH group (9.06 ± 2.52, 9.51 ± 3.61 and 11.42 ± 3.91 mmol/l, respectively, for all p < 0.001). The dinner 2 hr post-prandial glucose values were similar both in the lispro plus metformin and in the lispro plus NPH groups but were significantly lower as compared with regular insulin plus NPH group (8.36 ± 2.62, 8.97 ± 3.57 and 11.11 ± 4.15 mmol/l, respectively, for all p < 0.001). The bedtime glucose values were significantly lower in the lispro plus metformin group as compared with lispro plus NPH group (8.03 ± 2.55 vs 9.21 ± 3.52 mmol/l, p = 0.007) and regular insulin plus NPH group (8.03 ± 2.55 vs 10.23 ± 4.16 mmol/l, p < 0.001). Between lispro plus NPH and regular</p>	
--	--	--	--	--	--	--	--	--	--

								<p>insulin plus NPH groups, there was a significant difference ($p < 0.05$)</p> <p>When changes in BG levels in lispro plus metformin group were evaluated, 1 hr morning post-prandial, 1 hr lunch post-prandial and dinner 1 hr post-prandial BG levels were significantly decreased ($p = 0.006$), $p = 0.012$ vs $p = 0.043$ respectively). When changes in BG levels were evaluated in lispro plus NPH groups, changes in fasting and post-prandial glucose levels were statistically significant (for all parameters $p < 0.001$). When changes in BG were evaluated in regular insulin plus NPH group, changes in BG levels were statistically significant ($p < 0.001$), except changes in morning FBG levels.</p> <p>Glycosylated haemoglobin</p> <p>Lispro insulin plus NPH insulin was the most effective treatment regimen in controlling HbA_{1c} (lispro insulin plus NPH insulin vs lispro insulin plus metformin, $p = 0.013$; lispro insulin plus NPH insulin vs regular insulin plus NPH insulin, $p = 0.001$ and lispro insulin plus metformin vs regular insulin plus NPH insulin, $p > 0.05$). When comparison was made in each group, change in HbA_{1c} was statistically significant for all</p>	
--	--	--	--	--	--	--	--	---	--

								<p>groups (-3.18%, p = 0.001, -2.02%, p = 0.043 and -2.66, p = 0.008 respectively).</p> <p>HbA_{1c} (end of the study): Levels were 7.4 ± 0.3% in lispro plus metformin group, 6.7 ± 0.5% in the lispro plus NPH and regular insulin and NPH 7.5% ± 0.2. There was a difference between lispro plus metformin vs lispro plus NPH (p=0.013) and lispro plus NPH vs regular insulin plus NPH (p = 0.001).</p> <p>Within group comparisons before and after treatment Lispro plus metformin. The only significantly lower values were for HbA_{1c} and triglyceride levels (p = 0.043 for both) Lispro plus NPH. The only significantly lower values were for HbA_{1c} (p=0.001)¹ Regular insulin plus NPH. Only changes in HbA_{1c}, BMI, HDL cholesterol and triglyceride levels were statistically significant (p = 0.008, p = 0.029, p = 0.049 and p = 0.038 respectively).</p> <p>Hypoglycaemic events Observed percentage of hypoglycaemia was 0.4% in lispro plus metformin group, 0.57% in lispro plus NPH group and 0.009% in regular insulin plus NPH. (A BG level <60 mg/dl was considered hypoglycaemia). The difference</p>	
--	--	--	--	--	--	--	--	---	--

								among groups was statistically significant (p = 0.0120). At endpoint, the mean rates of hypoglycaemic episodes per patient were low in regular insulin plus NPH group. CHECK THIS (abstract different from results) ¹ BMI significant difference report but p = 0.11
Kabadi MU, Kabadi UM. Efficacy of sulfonylureas with insulin in type 2 diabetes mellitus. Annals of Pharmacotherapy 2003; 37(11):1572-1576. Ref ID: 110	RCT 1-	N=40	Patients with type 2 diabetes manifesting lapse of glycaemic control while receiving various individual sulfonylurea drugs Exclusion criteria: Patients with liver dysfunction and renal dysfunction	N=8 Tolazimeide group. 1g per day N=8 Glyburide group. 20 mg per day N=8 Glipizide GITS group. 20 mg per day N=8 Glimperide GLIM group. 8mg per day Insulin therapy: Each patient received an 10 units of premixed 70% NPH and 30% regular insulin in addition to the SU agent. Daily insulin dose was adjusted until a target was reached of 140-	N=8 placebo group (2 patients from each group) continued to receive their normal SU agent with placebo	6 months	<ul style="list-style-type: none"> • Insulin dose • Hypoglycaemic episodes • Weight gain • Fasting plasma C-peptide concentrations 	Insulin dose Patients receiving SU plus insulin required significantly lower (p < 0.01) daily insulin dose, total as well as units per kilogram of body weight. (BW) than placebo (55 vs 82 units/d). However, the daily insulin dose, total as well as units/kg BW, was significantly lower in subjects receiving GLIM in comparison to those receiving tolazamide, glyburide, or glipizide GITS (compared to other SU agents plus insulin p<0.05 and compared to placebo p<0.01) Hypoglycaemic episodes and weight gain The number of hypoglycaemic episodes during the last four weeks of the study was significantly lower in subjects receiving SU agents in comparison to placebo (1.68 vs 2.87; p < 0.01). The mean increase in bodyweight (kg) was significantly lower in the SU groups than placebo (2.4 vs 4.5;

				160 mg/dL (at 4 weeks)				<p>p<0.01). There was no significant difference between the individual agents on either measure.</p> <p>Fasting plasma C-peptide concentrations</p> <p>These declined significantly (p < 0.05) in all treatment groups, with the highest reduction in the placebo group. The magnitude of C-peptide suppression was significantly greater (p < 0.05) in the placebo group compared with the SU groups. There was no significant difference between the individual agents</p>	
<p>Kokic S B. Lispro insulin and metformin versus other combination in the diabetes mellitus type 2 management after secondary oral antidiabetic drug failure. Collegium Antropologicum 2003; 27(1):181-187. Ref ID: 313</p>	RCT 1-	N=87 -	<p>Patients with type 2 diabetes with secondary oral antidiabetic drug failure defined as HbA_{1c} value >8.5% fasting blood glucose values >8.9 mmol/l in more than 20% of all recorded glucose values and/or glucose values >10 mol/l before meal after maximal doses of a sulphonylurea during a minimal period of three months before starting the study. The study population (means)</p>	<p>N=29 Group 3: Combination of three daily doses of lispro and metformin (MFM) (combination group)</p>	<p>N=29 Group 1: Glimperide (GLIM) plus MFM (OHA group)</p> <p>N=29 Group 2: Two daily doses of biphasic insulin 30/70 with bedtime NPH insulin (insulin group)</p>	3 months	<ul style="list-style-type: none"> Glycemic profile (fasting and (FBG) postprandial glucose and HbA_{1c}) 	<p>HbA_{1c}</p> <p>The baseline value of HbA_{1c} was significantly different among groups ($\chi^2=6.71$, p=0.035). The combination group had a higher HbA_{1c} than the other two groups (9.21% ± 1.72%; 9.21 ± 1.54%; 10.0% ± 1.7% in the OHA, insulin and combination groups respectively) (p < 0.05). Three months later the value of HbA_{1c} had changed in all three groups (8.52% ± 1.70; 8.03 ± 1.05%; 8.00% ± 0.63% in the OHA, insulin and combination groups respectively) (p<0.05). At end point HbA_{1c} decreased significantly by similar values in all groups, with no statistical significance</p> <p>FBG</p>	None

			<p>was:</p> <ul style="list-style-type: none"> • 40.2% male • age 62.3 yrs • duration of diabetes 9.8 yrs • BMI 30.1 kg/m² 					<p>There was an improvement in FBG in all groups but the differences from baseline to end-of-trial were not significantly different. The fall of postprandial glucose from beginning to the end of the study was higher in the combination group 4.31 ± 3.4 mmol/l (-26.06 ± 22.05%); than in the insulin group 1.55 ± 3.9 mmol/l (-5.6% ± 34.7%) and in the OHA group 1.66 ± 3.76 mmol/l (-9.72 ± 36.85%) ($\chi^2=10.3$, p=0.006).</p>	
<p>Olsson PO, Lindstrom T. Combination-therapy with bedtime nph insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. Diabetes & Metabolism 2002; 28(4:Pt 1):272-277. Ref ID: 136</p>	RCT 1-	N=16	<p>Patients with type 2 diabetes who were not controlled on oral hypoglycaemic agents (OHA) (HbA_{1c} values 7.0-10.0%). Patients had been educated in the primary care diabetes programme and treated with oral agents for a minimum of 12 mths. The study population (means) was: 37.5% male. age 62 yrs body weight 71.3 kg BMI 24.6 kg/m² treated with OHA</p>	<p>N=8 Bedtime NPH insulin combined with daytime sulphonylurea (SU) (combination group) Target preprandial blood glucose concentrations were 4-7 mmol/l and postprandial values (1.5-2 hrs after a main meal) below 10 mmol/l.</p>	<p>N=8 Twice daily injections of a premixed combination of regular human insulin and NPH alone (twice daily insulin)</p>	24 weeks	<ul style="list-style-type: none"> • Insulin dose • HbA_{1c} • Body weight • C-peptide • Lipoprotein concentrations 	<p>Insulin dosage The twice daily insulin group were treated with a total insulin dose of 42.1 ± 3.6 U after 12 weeks and with slightly higher dose at week 24; 45.8 ± 4.2 U (p < 0.01). The corresponding insulin doses in the combination group were 17.0 ± 2.0 U after 12 weeks and 29.4 ± 5.4 U after 24 weeks. They were significantly lower in the combination group than in the twice daily insulin group (p = 0.0001 and 0.03 respectively). In the twice daily insulin group the initial insulin dose was 0.56 ± 0.07 U/kg body weight at week 12 and 0.61 ± 0.07 at week 24 while in the combination group 0.25 ± 0.03 U/kg body weight and 0.33 ± 0.05 U/kg body weight given respectively (in both instances p</p>	None

for 7.1 ± 1.3 yrs
Metformin was
withheld during the
study.

< 0.01 between treatments). No case of severe hypoglycaemia occurred during the study.

HbA_{1c}

HbA_{1c} was significantly lower in both groups at the end of the trial, combination group (8.3 vs 7.0, p <0.05) and insulin twice daily (8.3 vs 6.8, p < 0.03).

The difference between the groups was not significant

Body weight

In the first 12 weeks, body weight increased in the twice daily insulin group by 4.6 ± 0.85 kg and 1.8 ± 1.0 kg in the combination group (p < 0.05).

During weeks 12-24 there was a further increase of 1.1 ± 0.55 kg in the insulin twice daily group but only an increase of 0.1 ± 0.4 kg in the combination group (p=NS).

Overall, during the study, there was an increased with 5.8 ± 0.95 kg in the twice daily insulin and with 1.9 ± 1.0 kg in the combination group (p < 0.02 between treatments).

C-peptide

Both fasting and glucagon stimulated concentrations decreased significantly after 24 weeks in the combination group (0.79 ± 0.18 vs 0.56 ± 0.14 and 1.23 ± 0.22 vs 0.89 ± 0.17, respectively, p < 0.01). In the twice daily insulin group the difference was significant for the stimulated concentration only

								(1.23 ± 0.47 vs 0.98 ± 0.38, p = 0.05). There was a significant correlation between the baseline C-peptide concentration and the change of HbA _{1c} between baseline and week 24 in the combination group (p < 0.05, R ² 0.52) but no correlation was found in the twice daily insulin group. Lipoprotein concentrations Mean plasma lipoprotein concentrations were increased when determined before starting insulin treatment and reduction of total triglyceride concentration found in both groups did not reach significance.	
Zargar AH, Masoodi SR, Laway BA, Wani AI, Bashir MI. Response of regimens of insulin therapy in type 2 diabetes mellitus subjects with secondary failure. Journal of the Association of Physicians of India 2002; 50(5):641-646. Ref ID: 142	RCT 1-	N=188	Patients with type 2 diabetes with secondary sulfonylurea failure who failed to respond to maximum doses of glibenclamide (GBC) and phenformin (PFM). Inclusion criteria: More than 40 yrs and less than 70 yrs Fasting blood glucose (FBG) > 140 mg/dl at least twice on a regimen of appropriate diet	N=49 Group B (Insulin two doses plus GBC): GBC 10 mg twice daily continued and two doses of either intermediate acting or premixed insulin given at 8 am and 8 pm N=43 Group C (Morning insulin plus GBC): GBC 10 mg twice daily continued and one dose of intermediate	N=50 Group A (Insulin two doses): Two doses of intermediate acting insulin or combination of rapid and intermediate acting insulin at 8 am and 8 pm Protocol as for intervention	12 weeks	<ul style="list-style-type: none"> • Insulin dose • Blood glucose • Serum cholesterol and triglycerides • Weight and BMI 	Insulin dose Dose of insulin per kg body weight per day was 0.83 ± 0.07 and 0.86 ± 0.09 in groups A and B, and 0.46 ± 0.04 and 0.39 ± 0.03 in groups C and D respectively (A and B vs C and D, p < 0.001). Hospital stay was 8.42 ± 0.34, 11.95 ± 1.11, 8.59 ± 0.61 and 7.10 ± 0.48 in groups A, B, C and D respectively (p = 0.013). For group D, insulin dose and hospital stay required to achieve an acceptable FBG was marginally less (p < 0.001 and > 0.05) respectively. Blood glucose At follow-up, acceptable FBG (70-130 mg/dl) was achieved in	None

			<p>with 20 mg GBC and 100 mg PFM</p> <p>The Exclusion criteria included: Nephropathy Infections Coronary artery disease epilepsy</p> <p>The study population was mean age 54.5 yrs with 37.2% male. Mean weight was 54.2 kg and BMI 22.68</p>	<p>acting insulin given at 8 am</p> <p>N=46 Group D (Evening insulin PM plus GBC): single dose of intermediate acting insulin given at 8 pm and GBC 10 mg twice daily continued.</p> <p>Subjects were admitted to the endocrinology ward and discharged after reproducing acceptable FBG at least twice. A change in insulin regimen was avoided unless the patient reported hypoglycaemic symptoms with documentation of hypoglycaemia (blood glucose \leq 50 mg/dl) or FBG \geq 160 mg/dl.</p>				<p>19%, 26%, 31% and 46% of subjects in groups A, B, C and D respectively. There were no significant differences between the groups. An acceptable level of postprandial blood glucose ($<$ 200mg/dl) was achieved in only 23%, 14%, 15% and 37% of subjects in groups A, B, C and D respectively. There were no significant differences between the groups.</p> <p>Serum cholesterol and triglycerides</p> <p>At follow-up, in all regimens there was a significant increase in total cholesterol ($p < 0.05$). NB text and tables do not match.</p> <p>Weight and BMI</p> <p>Only group C showed a significant change from baseline, with an increase in weight at end of trial (50.18 ± 2.02 vs 58.83 ± 1.69, $p < 0.01$) and BMI (21.88 ± 0.95 vs 24.87 ± 0.83, $p < 0.01$).</p>	
--	--	--	---	---	--	--	--	--	--