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**Orignial Article**

# Clinical use and efficacy of the biphasic insulin Humalog Mix50 in people with insulin treated diabetes – a nationwide evaluation of clinical practice

N.K. Mungreiphy, J. Mamza, A.F. Lakhdar, M. Bannister, J. Elliott, I. Idris

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***Abstract***

Objectives: This study aims to investigate the metabolic effects of Humalog Mix50 in routine clinical practice. 229 patients ≥18 years old with diabetes, newly treated Humalog Mix50, were sourced from 6 secondary care services in the England.

Methods: Detailed clinical parameters were compared at baseline, 3 and 6 months post initiation. Responders was defined as HbA1c <7.5% (58mmol/mol) and/or HbA1c reduction of >1% (11mmol/mol) at 6 months.

Results: HbA1c showed significant reduction: -0.93%(-10mmol/mol) and -1.2% (-13mmol/mol) at 3 and 6 months respectively, while no significant change was noted for all the other parameters. When analysed according to frequencies of injections/day, greatest reduction was observed with the three-times a day regimen -1.0% (-11.0mmol/mol) and -1.3% (-14.6mmol/mol) at 3 and 6 months respectively]. HbA1c reduction was greatest in the group who previously received a basal-bolus insulin regimen: [-0.8% (-9.0mmol/mol) and -1.5% (-16.2mmol/mol) at 3 and 6 months respectively]. Reduction in weight was observed at 3 months (-1.8kg±4.3) only for those who were previously on a basal-bolus insulin regimen. Insulin doses increased following conversion to Humalog Mix50, irrespective of the types of insulin used prior Humalog Mix50, but not associated with weight gain. The independent predictors of response to Humalog Mix50, were baseline HbA1c, Caucasian, presence of nephropathy, prior use of basal-bolus insulin and prior use of other premixed combination.

Conclusion: Humalog Mix50 is therefore an effective therapeutic option for achieving glycaemic control in patients with suboptimal HbA1c levels, especially among those who were previously on basal-bolus insulin regimen and those who received it three times daily, with a neutral effect on weight parameters.

Limitations: This was a retrospective study of routine clinical practice and is therefore limited by allocation bias andsome missing data.Information on rates of hypoglycaemia and quality of life are not available.

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# Clinical use and efficacy of the biphasic insulin Humalog Mix50 in people with insulin treated diabetes – a nationwide evaluation of clinical practice

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*Key words:* Humalog mix50; Insulin; Routine clinical practice; HbA1c

***[Short title:*** Clinical use and efficacy of the biphasic insulin Humalog Mix50]

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Humalog Mix50, but not associated with weight gain. The independent predictors of response to Humalog Mix50, were baseline HbA1c, Caucasian, presence of nephropathy, prior use of basal-bolus insulin and prior use of other premixed combination.

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## Introduction

There is currently no consensus about the most appropriate insulin regimen to be chosen in people with diabetes [1]. NICE guidelines however recommend initiating insulin therapy with human neutral protamine Hagedorn (NPH) insulin or a long-acting analogue (basal insulin) injected at bed-time or twice daily according to the patient's need. [2] Thereafter, therapy can be intensified with prandial insulin (which may include a premixed therapy or basal-bolus regimen). While such basal-bolus insulin is widely regarded as the 'gold standard' insulin regimen in people with diabetes, the technicalities of this regimen coupled with the need for frequent insulin

dose adjustment resulted in our observation that in routine practice, glycaemic control remains suboptimal in many patients receiving a basal bolus insulin regimen. [3]

In people without diabetes, basal insulin secretion represents approximately 50% of insulin secretion, with the remaining 50% being meal related insulin secretion [4]. Among patients with type 2 diabetes requiring intensive insulin therapy regimens in the form of multiple daily injection or insulin pump therapy, both regimen required 50% basal and 50% rapid acting insulin following dose titration [5]. Based on these, biphasic insulin lispro 50/50 (Humalog Mix50) containing 50% rapid-acting and basal insulin respectively, was developed to provide the physiological advantages of rapid and basal insulin in the convenience of a premixed formulation [6]. Indeed, intensification of insulin therapy (where patients' blood glucose levels remain suboptimal after receiving biphasic insulin aspart 30/70, biphasic human insulin 30/70 or biphasic insulin lispro 25/75) has been shown to be achieved by switching to premixed regimens with greater prandial coverage (Humalog Mix50) [7,8,9]. There is however, limited post-market surveillance and/or real world evidence assessing how Humalog Mix50 is used in routine practice, as well as the effectiveness of this insulin regimen in patients with diabetes. This study specifically aims to investigate how this insulin is used in routine practice in the UK (e.g. first line, second line, third line insulin twice daily, thrice daily or in combination with prandial or basal insulin) as well as the effectiveness of Humalog Mix50 regimen in patients with diabetes.

## Methods

*Patient Selection and Analyses*

Anonymised retrospective information on 229 patients using Humalog Mix50 in clinical practice was received from 6 centres across England. Demographic data of the patients which includes ethnicity, gender, type of diabetes, year of diabetes diagnosis, hypoglycaemia unawareness, height, weight and medications were included in the audit. At baseline, patients were divided according to the type of diabetes for analyses. Information on complications like stroke, peripheral artery disease, retinopathy, nephropathy and neuropathy were also assessed. Data were collated at the third and sixth month post commencement of Humalog Mix50. All patients who had received Humalog Mix50 with available data for at least 6 months were eligible for inclusion.

Data on the current antidiabetic and insulin therapy with details of dosing frequency and year of start were noted. Information on antidiabetic therapy including insulin prior to Humalog Mix50 therapy and after starting Humalog Mix50 therapy at 3 and 6 months were evaluated. Comparison of the changes in the patients' HbA1c, eeight, BMI, eGFR, total cholesterol, triglyceride, HDL, LDL, systolic and diastolic BP prior to starting Humalog Mix50 therapy and Humalog Mix50 at 3 and 6 months post Humalog Mix50 initiation were calculated.

*Statistical Analysis*

Descriptive statistics are provided for patients according to their type of diabetes. Changes in HbA1c, weight, BMI, eGFR, total cholesterol, triglyceride, HDL, LDL, systolic and diastolic BP

from prior to starting Humalog Mix50 therapy and after starting Humalog Mix50 therapy at 3 and 6 months were evaluated using paired t-test. Analysis of variance (ANOVA) was used to check the variation in Mean (±SD) of different variables. p-values of <0.05 were considered to be statistically significant in the analyses.

ANOVA was applied to assess the effect of different dosing frequency of Humalog Mix50 therapy per day on the patients' HbA1c, weight, BMI, eGFR, total cholesterol, triglyceride, HDL, LDL, systolic and diastolic BP at the third and sixth months. Changes after starting Humalog Mix50 therapy at 3 and 6 months were also evaluated according to the patients' prior medication using ANOVA. Statistical analyses were performed using StataSE 11

**Results**

There were two hundred and twenty-nine patients with detailed baseline information. Demographic information of patients is shown in table 1. Most of the patients were Caucasian. Thirty two patients have type 1 diabetes while one hundred and ninety seven patients have type 2 diabetes, with mean type 2 diabetes duration of 18.35 (±7.9) years. Negligible amount of patients experienced hypoglycaemia unawareness . Mean HbA1c at baseline was 85mmol/mol (9.9%) and mean BMI was 34.8kg/$m^2$ (Table 1). Micro- and macro vascular complications were significantly more prevalent in patients with type 2 diabetes. The majority of patients (51.7%) received a premixed insulin therapy as their first insulin regimen. Prior to Humalog Mix50 therapy, most patients were on premixed insulin 30/70 (46.3%) and/or Metformin (47.2%) while few received Basal Bolus insulin (6.1%), Basal Acting (11.97%) or other oral therapy (14.4%)

such as Gliptins, Glucagon like peptide-1 analogues, sulphonylureas and thiazolidinediones. Most patients (40.4%) took Humalog Mix50 as their current insulin therapy three times daily with mean doses of 135.1 ± 75.3 units per day (1.4 ± 0.7 U/kg), followed by those (24.1% each) who took four times daily with mean doses of 90.6 ±62.7 units per day (0.93 ± 0.7 U/kg) and twice daily with mean doses of 90.6 ± 62.7 units per day (0.78 ± 0.4 U/kg). There were only 11.4% patients who had Humalog Mix50 once a day with mean dose of 46.1 ± 68.7 units per day (0.49 ±0.3 U/kg).

Table 2 shows the mean values of weight, BMI, HbA1c, GFR, total cholesterol, triglyceride, HDL, LDL, systolic and diastolic BP, prior to starting Humalog Mix50 therapy and at 3 and 6 months after starting Humalog Mix50. HbA1c showed significant reduction at both time points of investigation while no significant change was noted for all the other parameters following the initiation of Humalog Mix50 (Table 2). However, when changes in parameters at 3 and at 6 months were analysed according to frequencies of Humalog Mix50 injections per day, we observed significant differences for most parameters depending on the frequencies of Humalog Mix50 therapy being used (Table 3). HbA1c reduction was seen for all frequencies of Humalog Mix50 injection therapy (Figure 1), with the greatest reduction observed with the three times a day regimen. Patients who took Humalog Mix50 four times a day showed reduction of weight and BMI at both 3 and 6 months, whereas patients with three and two times injections/day showed increment in the values. Total cholesterol and triglyceride levels were unchanged following initiation of Humalog Mix50.

The changes in weight, BMI, HbA1c, GFR, total cholesterol, triglyceride, HDL, LDL, systolic and diastolic BP after starting Humalog Mix50 therapy according to prior medication is reported in table 4. Among patients who were on basal bolus prior to Humalog Mix50 therapy, reduction in weight was observed at 3 months whereas the values increased at 3 and 6 months among those who were previously taking premix and basal insulin medication. HbA1c outcomes following Humalog Mix50 were significantly different depending on the insulin regimen used prior to Humalog Mix50. At 6 months, HbA1c reduction appears to be greatest in the group who previously received a basal bolus insulin regimen (Figure 2). Of note, in a separate subanalysis, similar outcome was observed among patients with type 2 diabetes as that from the whole cohort (result not presented here). Insulin doses increased following conversion to Humalog Mix50, irrespective of the types of insulin used prior to conversion to Humalog Mix50 (Table 5). The patient group who received the greatest amount of insulin were those who previously received a basal bolus insulin group prior to conversion to Humalog Mix50, (increase in insulin dose from 0.78u/kg to 1.2u/kg. Reassuringly, this was not associated with weight gain (Table 4).

Table 6 displays the logistic regression showing predictors of responders (n=170) versus non-responders (n=59) to Humalog Mix50 therapy. Responder was defined as HbA1c reduction by 1% or more at 3 months or 6 months or achieving HbA1c <7.5%% (58mmol/mol) at 6 months if baseline HbA1c >=7.5%(58mmol/mol). The response rate was 74%. The independent predictors of response to Humalog Mix50, after adjusting for other confounders were baseline HbA1c, Caucasian, presence of nephropathy and prior use of basal bolus insulin as well as prior use of other premixed combination (other than Humalog Mix50).

## Discussion

This audit of Humalog Mix50 provides useful insights into the current strategies in Humalog Mix50 prescribing as well as clinical effectiveness of this insulin in routine specialist clinical care in England. The audit also allowed some analyses of the predictors of good glycaemic responses to Humalog Mix50, comparisons between different frequencies of Humalog Mix50 being prescribed, as well as analyses of effectiveness and weight outcome, based on previous insulin regimen used prior to Humalog Mix50.

As a whole, this audit suggests that biphasic insulin regimen mix30 appears to be the most widely used first line insulin regimen in clinical practice. When prescribed, Humalog Mix50 is often prescribed as a third or 4$^{th}$ line insulin regimen and is associated with a reduction in HbA1c at 3 and at 6 months. The rate of responders to Humalog Mix50 - based on our strict definition of responders, (reduction in HbA1c by >1% or achieving HbA1c target of <7.5%(58mmol/mol), observed in this study was very high (74%), compared with only 35% of patients who responded to this insulin regimen seen in our previous study [10]. This may reflect the fact that the data from this audit was derived from data from specialist centres, whereas our previous data was derived from a UK general practice dataset.

The majority of Humalog Mix50 is prescribed three times a day, which was also associated with the highest insulin dose/kg of insulin, compared with other frequencies of Humalog Mix50 injection. This frequency of insulin injection is associated with weight gain. Although insulin intensification is widely recognised to be associated with weight gain [11,12], previous data has shown favourable effects of Humalog Mix50 regimen on weight [10,13]. No difference in

HbA1c reduction was observed across different frequencies of Humalog Mix50 injections, although greatest HbA1c reduction was observed among those who were prescribed three times day. In line with this, previous studies have shown benefits of Humalog Mix50 compared to human insulin 70/30 or Humalog 75/25 [9,13] in reducing post-prandial glucose excursion [6]. These benefits were augmented when Humalog Mix50 is given thrice daily compared with 70/30 twice daily [9] or 70/30 thrice daily [14], but equivalent when compared with a basal bolus insulin regimen [15].

When analysed according to the previous insulin regimen being used, those who converted to Humalog Mix50 from a previous basal bolus insulin regimen appears to show the greatest reduction in HbA1c, compared with those who was previously on a biphasic 30 or a long acting only insulin. The reason for this is unclear, and is out of the scope of this audit. It is tempting to speculate that the complexities of a basal bolus insulin regimen when prescribed in obese patients with diabetes (such as in this patient cohort), is associated with reduced treatment compliance and hence treatment failure. To this end, converting these patients to a more fixed biphasic insulin regimen, with an appropriate prandial insulin cover might be beneficial. Indeed, previous use of basal bolus insulin (along with the recognised, baseline HbA1c) is an independent predictor of success to Humalog Mix50 regimen. Presence of diabetic nephropathy, perhaps by virtue of declining GFR and increased risks of hypoglycaemia is also a predictor of response to Humalog Mix50. Of note however, the patient group who received the greatest amount of insulin were those who previously received a basal bolus insulin group prior to conversion to Humalog Mix50, (increase in insulin dose from 0.78u/kg to 1.2u/kg), but this was not associated with weight gain. The explanation in the discordance between weight loss (at 3months) and increased insulin dose unfortunately is outside the remit of this study, but we

would speculate that changes in lifestyle, compliance to treatment and eating habits from converting from a 4 injections a day to a fixed three injections per day may somewhat play a role in this.

The magnitude of HbA1c reduction in this cohort was similar to that previously observed in the national exenatide audit in patients not on insulin [17]. However, in the same audit, HbA1c reduction was much less at three months among those who were on insulin and continued on insulin therapy (-0.51%) or among patients who discontinued insulin therapy following initiation of exenatide [17]. Patients in the previous exenatide audit however consisted entirely of patients with type 2 diabetes and were therefore slightly heavier (BMI 40.3, 40.2 and 39.4 respectively for different groups) than patients in this present audit (mean BMI 34.8kg/$m^2$).

This analysis had several limitations. Firstly, there was incomplete HbA1c and weight data due to problems of an audit in real-life clinical practice (e.g. missed follow-up, missed measurements or incomplete data entry). This has the potential of introducing bias among available results. Secondly, variability in clinical practice would influence insulin intensification strategy between centres. It important to note however that all data were collected from specialist centres with patients receiving input by specialist clinicians. We were also unable to determine treatment compliance and variations in structured education programmes that patients may or may have not received. We also did not distinguish between type 1 and type 2 diabetes in our analysis because the small number of patients with type 1 diabetes in this data would limit any meaningful conclusion to patients with type 1 diabetes. However, where appropriate, we performed subanalysis in patients with type 2 diabetes alone, and the result was similar to the whole cohort. In addition, other than metabolic outcome, the aim of this study is look at prescribing pattern of Humalog Mix50 among all insulin treated patients with diabetes. Finally, data on quality of life

and hypoglycaemia is not available in this study. This is crucial, since any possible improvement in HbA1c, maybe driven by reduction in the frequency of insulin treatment, hypoglycaemia risks or lack of need to adjust insulin doses according to carbohydrate load.

## Conclusion

Conversion to Humalog Mix50 regimen appears to be a reasonable therapeutic option among patients who are already on insulin therapy, with suboptimal glucose control. Although the glycaemic response of this insulin regimen is heterogeneous; patients who were previously on a basal bolus insulin regimen and those who received three times a day Humalog Mix50 appeared to benefit most with a neutral effect on weight parameters.

## Transparency

*Declaration of funding:*

This study was funded by an un-restricted grant from Eli Lilly Pharmaceutical. Eli Lilly provided no further input in data acquisition, data access, analysis and interpretation of the data.

*Declaration of financial/other relationships:*

II has received research grants and speakers fees from Eli Lilly and Novo Nordisk. JE and AL have received speaker fees from Eli Lilly, MSD, Novo Nordisk, Sanofi, and have also received advisory board fees from Sanofi. MB has received speaker fees from Eli Lilly, Boehringer Ingleheim, and advisory board fees from Novo Nordisk. CMRO Peer Reviewer 1 has no relevant financial or other relationships to disclose. CMRO Peer Reviewer 2 has received grants from the Russian Scientific Foundation; is a consultant to and the National coordinator of RTCs for AstraZeneca and AbbVie; and is on the Speakers' Bureau of Eli Lilly, Novartis, Novo Nordisk, MSD and AztraZeneca.





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Table 1: Demographic and baseline characteristics of the patients

| **Variables (%)** | **Total (n=229) / Mean (SD)** | **Type 1 Diabetes (n=32)** | **Type 2 Diabetes (n=197)** | **p-Value** |
|---|---|---|---|---|
| **Ethnicity** | | | | |
| Caucasian | 166 (72.4) | 29 (17.5) | 137 (82.5) | |
| Non-Caucasian | 63 (27.6) | 3 (4.76) | 60 (95.2) | 0.013 |
| **Gender** | | | | |
| Males | 117 (51.1) | 19 (16.24) | 98 (83.8) | |
| Females | 112 (48.9) | 13 (11.6) | 99 (88.4) | 0.312 |
| **Hypoglycaemia unawareness** | | | | |
| Yes | 25 (11.7) | 10 (40) | 15 (60) | |
| No | 188 (88.3) | 20 (10.6) | 168 (89.3) | <0.001 |
| **Complications** | | | | |
| Stroke | 20 (8.7) | 0 | 20 (100) | 0.034 |
| Peripheral Artery | 35 (15.3) | 0 | 35 (100) | 0.004 |
| Retinopathy | 138 (60.3) | 17 (12.3) | 121 (87.7) | 0.029 |
| Nephropathy | 102 (44.5) | 7 (6.9) | 95 (93.1) | <0.001 |
| Neuropathy | 104 (45.4) | 5 (4.8) | 99 (95.2) | <0.001 |
| **First insulin regimen** | | | | |

| **Variables (%)** | **Total (n=229) / Mean (SD)** | **Type 1 Diabetes (n=32)** | **Type 2 Diabetes (n=197)** | **p-Value** |
|---|---|---|---|---|
| HumalogMix50 | 27 (18.1) | 2 (7.4) | 25 (92.6) | |
| Basal Insulin | 36 (24.2) | 6 (16.7) | 30 (83.3) | |
| Premixed | 80 (53.7) | 10 (12.5) | 70 (87.5) | |
| Short acting | 6 (4.0) | 1 (16.7) | 5 (83.3) | 0.735 |
| **Mean Age** (years) | 63.18 (12.6) | 52.84 (18.2) | 64.86 (10.5) | <0.001 |
| **Diabetes duration** (years) | 19.12 (9.4) | 24.1 (15.2) | 18.35 (7.9) | <0.001 |
| **Duration of insulin regimen** (years) | 11.41 (9.2) | 21.71 (15.9) | 9.64 (6) | <0.001 |
| **Height** (m) | 1.66 (0.1) | 1.68 (0.1) | 1.66 (0.1) | 0.805 |
| **Weight** (kg) | 96.76 (23.9) | 81.02 (17.6) | 99.15 (23.9) | 0.049 |
| **BMI** ($kg/m^2$) | 34.8 (7.8) | 28.48 (5.8) | 35.81 (7.6) | 0.086 |
| **HbA1c** (%) | 9.9 (2.1) | 9.64 (2.2) | 9.95 (2.0) | 0.568 |
| **HbA1c** (mmols/mol) | 85 (23) | 82 (24) | 85 (21.9) | 0.568 |
| **eGFR** ($mls/min/m^2$) | 69.76 (63) | 78.46 (23.4) | 68.35 (67.2) | <0.001 |
| **Total cholesterol** (mmol/L) | 4.31 (1.1) | 4.51 (1.1) | 4.28 (1.1) | 0.922 |
| **Triglyceride** (mmol/L) | 2.50 (1.6) | 1.76 (1.8) | 2.63 (1.5) | 0.217 |
| **HDL** (mmol/L) | 1.19 (0.4) | 1.57 (0.46) | 1.12 (0.4) | 0.091 |
| **LDL** (mmol/L) | 2.05 (0.8) | 2.12 (0.8) | 2.03 ( 0.9) | 0.617 |
| **Systolic BP** (mmHg) | 138.24 (18.8) | 128.07 (11.7) | 139.84 (19.2) | 0.002 |
| **Diastolic BP** (mmHg) | 73.88 (11.1) | 72.47 (8.03) | 74.10 (11.5) | 0.02 |

Values are quoted as count/actual numbers (%) or as mean (± sd.)

Table 2: Mean of the variables prior to starting Humalog Mix50 therapy and at 3rd and 6th months after starting Humalog Mix50 along with the differences of the means and level of significance

| **Variables** | Prior to starting Humalog Mix 50 therapy | | 3 months after starting Humalog Mix50 | | Differences in 3 months | | 6 months after starting Humalog Mix50 therapy | | Differences in 6 months | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean (sd) | n | Mean (sd) | Mean change (3rd month-prior) | p-value | n | Mean (sd) | Mean change (6th month-prior) | p-value |
| **Weight** (kg) | 220 | 96.8 (23.9) | 139 | 94.8 (23.8) | -1.04 (4.6) | 0.451 | 194 | 97.9 (25.9) | 1.0 (9.6) | 0.657 |
| **BMI** (kg/m$^2$) | 213 | 34.8 (7.8) | 135 | 34.6 (8.7) | -0.42 (1.8) | 0.850 | 187 | 35.4 (8.8) | 0.41 (3.4) | 0.441 |
| **HbA1c** (%) | 227 | 9.9 (2.1) | 159 | 9.2 (1.7) | -0.93 (1.6) | 0.001 | 210 | 8.7 (1.7) | -1.18 (1.9) | P<0.001 |
| **HbA1c** (mmols/mol) | 227 | 85 (23.0) | 159 | 77 (18.6) | -10.2 (17.5) | 0.001 | 210 | 73 (18.6) | -12.9 (20.8) | P<0.001 |
| **eGFR** (mls/min/m$^2$) | 214 | 69.8 (63) | 133 | 66.3 (25.2) | -.94 (11.2) | 0.544 | 181 | 67.7 (67.8) | -2.28 (89.1) | 0.750 |
| **Total cholesterol** (mmol/L) | 210 | 4.3 (1.1) | 111 | 4.3 (1.3) | -0.01 (.8) | 0.715 | 168 | 4.3 (1.0) | -0.05 (.9) | 0.858 |
| **Triglyceride** | 188 | 2.5 (1.6) | 100 | 2.6 (1.7) | -0.13 (1.2) | 0.845 | 149 | 2.3 (1.5) | -0.30 (1.2) | 0.265 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (mmol/L) | | | | | | | | | | |
| **HDL** (mmol/L) | 169 | 1.2 (0.4) | 85 | 1.2 (0.4) | 0.01 (0.3) | 0.853 | 141 | 1.2 (.4) | -0.02 (.3) | 0.820 |
| **LDL** (mmol/L) | 127 | 2.1 (0.8) | 66 | 2.1 (0.7) | -0.01 (.7) | 1.000 | 108 | 2.0 (.7) | -0.06 (.8) | 0.774 |
| **Systolic BP** (mm/Hg) | 221 | 138.2 (18.8) | 132 | 135.1 (16.7) | -0.29 (17.0) | 0.109 | 183 | 137.4 (17.9) | -0.13 (20.4) | 0.633 |
| **Diastolic BP** (mm/Hg) | 221 | 73.8 (11.1) | 132 | 74.60 (9.9) | 0.65 (11.6) | 0.540 | 183 | 73.1 (11.1) | -1.04 (11.5) | 0.488 |

Table 3: Changes after starting Humalog Mix50 therapy at 3rd and 6th months according to frequency per day

| **Variables** | **Mix50 Freq per day** | Mean change in variables at 3 months (3 months & prior) | | | Mean change in variables at 6 months (6 months & prior) | | |
|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Freq | p-value | Mean (SD) | Freq | p-value |
| Weight (kg) | Four Times | -.83 (2.5) | 13 | | -1.92 (18.2) | 37 | |
| | Three Times | .91 (4.9) | 72 | | 2.26 (6.6) | 84 | |
| | Two times | 1.73 (3.5) | 40 | | 1.50 (4.1) | 48 | |
| | Once | 1.51 (7.2) | 13 | | -.06 (4.8) | 21 | |
| | Total | 1.04 (4.6) | 138 | <0.001 | 1.00 (9.6) | 190 | <0.001 |
| BMI ($kg/m^2$) | Four Times | -.29 (.9) | 13 | | -.66 (6.3) | 36 | |
| | Three Times | .38 (1.9) | 72 | | .89 (2.5) | 83 | |
| | Two times | .69 (1.2) | 37 | | .56 (1.5) | 45 | |
| | Once | .61 (2.9) | 12 | | -.01 (1.8) | 20 | |
| | Total | .42 (1.8) | 134 | <0.001 | .41 (3.4) | 184 | <0.001 |
| HbA1c (%) | Four Times | -.90 (1.6) | 21 | | -.92 (2.4) | 42 | |
| | Three Times | -1.01 (1.5) | 78 | | -1.34 (1.7) | 90 | |
| | Two times | -0.89 (1.8) | 46 | | -1.13 (2.0) | 51 | |
| | Once | -0.52 (0.9) | 11 | | -1.20 (2.0) | 24 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total | -0.92 (1.8) | 156 | 0.089 | -1.18 (1.9) | 207 | 0.069 |
| GFR | Four Times | -6.51 (21.2) | 15 | | -3.23 (199.8) | 35 | |
| (mls/min/$m^2$) | Three Times | 1.17 (9.0) | 66 | | -2.27 (16.5) | 78 | |
| | Two times | -1.63 (6.4) | 38 | | -2.5 (9.4) | 42 | |
| | Once | -4.55 (15.3) | 10 | | -.19 (17.8) | 20 | |
| | Total | -.99 (11.2) | 129 | <0.001 | -2.28 (89.3) | 175 | <0.001 |
| Total choles- | Four Times | .11 (.5) | 17 | | -.09 (1.0) | 35 | |
| terol | Three Times | -.04 (.9) | 55 | | -.07 (.9) | 71 | |
| (mmol/L) | Two times | -.05 (.8) | 29 | | -.05 (.8) | 35 | |
| | Once | .20 (.3) | 5 | | .13 (1.1) | 19 | |
| | Total | -.01 (.8 ) | 106 | 0.011 | -.05 (.9) | 160 | 0.344 |
| Trigly-ceride | Four Times | -.54 (.8) | 11 | | -.32 (1) | 25 | |
| (mmol/L) | Three Times | -.07 (1.2) | 50 | | -.30 (1.4) | 62 | |
| | Two times | .02 (1.3) | 26 | | -.29 (1.1) | 29 | |
| | Once | -.42 (.6) | 5 | | -.25 (1.1) | 17 | |
| | Total | -.12 (1.2) | 92 | 0.157 | -.30 (1.2) | 133 | 0.092 |
| HDL | Four Times | -.03 (.6) | 16 | | -.09 (.5) | 34 | |
| (mmol/L) | Three Times | .01 (.2) | 35 | | -.03 (.2) | 43 | |
| | Two times | .04 (.2) | 20 | | .03 (.2) | 26 | |
| | Once | 0 (.1) | 4 | | .04 (.2) | 18 | |
| | Total | .01 (.3) | 75 | <0.001 | -.02 (.3) | 121 | <0.001 |
| LDL | Four Times | .28 (.5) | 15 | | -.01 (.8) | 31 | |
| (mmol/L) | Three Times | -.08 (.9) | 26 | | -.21 (.7) | 28 | |
| | Two times | -.33 (.7) | 13 | | -.13 (.8) | 15 | |
| | Once | .25 (.1) | 4 | | .18 (1) | 16 | |
| | Total | -.02 (.8) | 58 | 0.007 | -.06 (.8) | 90 | 0.440 |
| Systolic BP | Four Times | -3.94 (24.18) | 16 | | -3.08 (22.69) | 37 | |
| (mm/Hg) | Three Times | -.33 (15.88) | 69 | | .12 (20.27) | 78 | |
| | Two times | 4.77 (15.17) | 35 | | 3.37 (20.07) | 43 | |
| | Once | -3.91 (16.74) | 11 | | -.85 (16.90) | 20 | |
| | Total | .29 (17.04 ) | 131 | 0.108 | .129 (20.36) | 178 | 0.558 |
| Diastolic BP | Four Times | 3.44 (16.05) | 16 | | -4.11 (11.46) | 37 | |
| (mm/Hg) | Three Times | -.93 (10.19) | 69 | | -.76 (10.40) | 78 | |
| | Two times | 1.91 (10.80) | 35 | | .09 (13.56) | 43 | |
| | Once | 2.45 (14.83) | 11 | | 1.05 (10.11) | 20 | |
| | Total | .65 (11.60) | 131 | 0.054 | -1.04 (11.45) | 178 | 0.211 |

Table 4: Changes after starting Humalog Mix50 therapy at 3rd and 6th months according to insulin medication prior to conversion to Mix50

| **Changes in Variable** | **Prior Medication** | Mean change at 3 months (3 months-prior) | | | Mean change at 6 months (6 months-prior) | | |
|---|---|---|---|---|---|---|---|
| | | Mean SD | Freq | p-value | Mean SD | Freq | p-value |
| Weight (kg) | Premix | 1.31 (4.1) | 60 | | .09 (12) | 83 | |
| | Basal Bolus | -1.79 (4.3) | 8 | | .09 (2.2) | 10 | |
| | Basal Ins | 1.46 (6) | 19 | | 1.15 (7.5) | 26 | |
| | Total | 1.06 (4.6) | 87 | 0.110 | .32 (10.6) | 119 | <0.001 |
| BMI ($kg/m^2$) | Premix | 0.49 (1.5) | 58 | | .04 (4.0) | 80 | |
| | Basal Bolus | -0.70 (1.7) | 8 | | .01 (.8) | 10 | |
| | Basal Ins | 0.54 (2.2) | 18 | | .40 (2.5) | 25 | |
| | Total | .39 (1.7) | 84 | 0.261 | .11 (3.5) | 115 | <0.001 |
| HbA1c (%) | Premix | -.64 (6.9) | 69 | | -.85 (1.7) | 93 | |
| | Basal Bolus | -.82 (0.7) | 9 | | -1.48 (1.3) | 11 | |
| | Basal Ins | -.43 (1.8) | 24 | | -.87 (2.6) | 30 | |
| | Total | -.06 (5.7) | 102 | 0.016 | -.91 (1.9) | 134 | 0.005 |
| GFR (mls/min/$m^2$) | Premix | -0.40 (12.9) | 61 | | -11.41 (94.3) | 80 | |
| | Basal Bolus | -7.54 (16.4) | 8 | | 2.21 (9.5) | 10 | |
| | Basal Ins | -2.81 (7.9) | 20 | | -3.07 (10.6) | 25 | |
| | Total | -1.59 (12.3) | 89 | 0.028 | -8.42 (78.8) | 115 | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Total cholesterol (mmol/L) | Premix | .18 (0.7) | 46 | | -.01 (.8) | 74 | |
| | Basal Bolus | .37 (0.4) | 3 | | -.16 (.6) | 8 | |
| | Basal Ins | .19 (0. 7) | 20 | | .27 (.6) | 23 | |
| | Total | .19 (0.7) | 69 | 0.632 | .04 (.8) | 105 | 0.088 |
| Triglyceride (mmol/L) | Premix | -.22 (1) | 37 | | -.20 (1.3) | 61 | |
| | Basal Bolus | -1.17 (1.1) | 3 | | -.64 (1.9) | 7 | |
| | Basal Ins | .55 (1.3) | 17 | | .02 (.7) | 19 | |
| | Total | -.04 (1.2) | 57 | 0.424 | -.19 (1.2) | 87 | 0.041 |
| HDL (mmol/L) | Premix | -.02 (.4) | 31 | | -.06 (.4) | 52 | |
| | Basal Bolus | .033 (.1) | 3 | | .04 (.1) | 5 | |
| | Basal Ins | .07 (0.2) | 11 | | .05 (.1) | 18 | |
| | Total | .002 (0.4) | 45 | 0.003 | -.03 (.3) | 75 | <0.001 |
| LDL (mmol/L) | Premix | .13 (.4) | 23 | | -.14 (.7) | 36 | |
| | Basal Bolus | .37 (.6) | 3 | | -.12 (.7) | 5 | |
| | Basal Ins | .55 (.4) | 4 | | .19 (.6) | 10 | |
| | Total | .21 (.4) | 30 | 0.822 | -.08 (.7) | 51 | 0.827 |
| Systolic BP (mm/Hg) | Premix | .93 (16.4) | 59 | | 1.71 (18.6) | 78 | |
| | Basal Bolus | -12.13 18.6) | 8 | | -9.1 (16) | 10 | |
| | Basal Ins | -3.29 (22.9) | 17 | | .5 (21.3) | 26 | |
| | Total | -1.17 (18.3) | 84 | 0.229 | .48 (19.1) | 114 | 0.541 |
| Diastolic BP (mm/Hg) | Premix | 2.68 (11.2) | 59 | | .23 (9.8) | 78 | |
| | Basal Bolus | -6.5 (16.6) | 8 | | -8.8 (13.1) | 10 | |
| | Basal Ins | -5.06 (13.3) | 17 | | -1.23 (13.3) | 26 | |
| | Total | 0.24 (12.6) | 84 | 0.273 | -.89 (11.2) | 114 | 0.107 |

Table 5: Total mean (sd) dose of insulin prior to Mix50 treatment = 84.7 (50.1) units/day or 0.88 (0.5) U/kg per day. OD= once daily, BD=twice daily, TDS=three times a day, QDS= four times a day

| | N(%) | Prior Insulin dose (Units/Kg/Day) Mean (SD) | N (%) | Baseline Mix50 dose (Units/Kg/Day) Mean (SD) | MD (Se) | P value |
|---|---|---|---|---|---|---|
| **Total** | 141 | 0.88 (0.5) | 215 | 1.03 (0.7) | 0.15 (0.07) | 0.01 |
| **Prior Regimen** | | | | | | |
| Basal bolus | 14 | 0.54 (0.3) | 14 | 0.80 (0.4) | 0.26 (0.1) | 0.03 |
| Basal insulin | 30 | 0.78 (0.5) | 31 | 1.20 (1.0) | 0.42 (0.2) | 0.02 |
| Other premixed | 97 | 0.96 (0.5) | 96 | 1.09 (0.6) | 0.13 (0.08) | 0.05 |
| **Frequency of Mix50** | | | | | | |
| OD | 24 | 0.41 (0.3) | 24 | 0.49 (0.3) | 0.08 (0.09) | 0.2 |
| BD | 95 | 0.98 (0.4) | 51 | 0.77 (0.4) | -0.21 (0.07) | 0.9 |
| TDS | 22 | 0.91 (0.5) | 88 | 1.38 (0.7) | 0.47 (0.2) | 0.002 |
| QDS | - | - | 52 | 0.93 (0.7) | | |

Table 6:

| **Predictors** | **OR 95% CI** | **p value** |
|---|---|---|
| **HbA1c (%)*** | 1.45 [1.21,1.74] | <0.001 |
| **Ethnicity** | | |
| Non-caucasian | 1.00 | - |

| | | |
|---|---|---|
| Caucasian | 1.87 [0.99,3.53] | 0.05 |
| **Nephropathy** | | |
| No | 1.00 | |
| Yes | 2.13 [1.06,4.27] | 0.03 |
| **Prior Insulin therapy** | | |
| Basal bolus | 3.67 [1.02,13.14] | 0.05 |
| Basal insulin | 1.46 [0.72,2.96] | 0.3 |
| Premixed (Non-HM50) | 2.89 [1.86,4.48] | 0.001 |

Table: Logistic regression showing predictors of responders (n=170) versus non-responders (n=59) to Humalog Mix50 therapy

*Responders: Predictor of response if HbA1c reduction by 1% or more at 3 months or 6 months or achieving HbA1c < 7% at 6 months if baseline HbA1c >=7.5%

Figure 1:

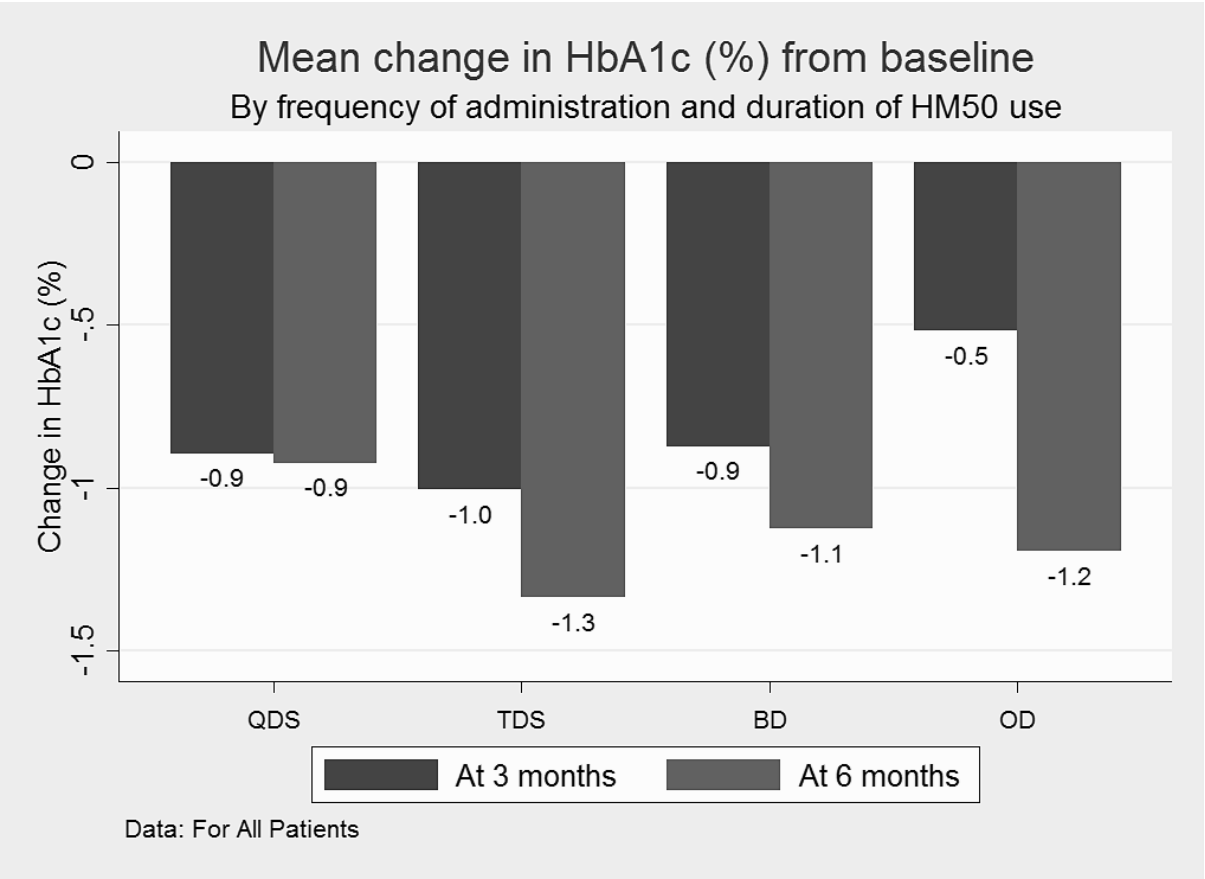


Figure 2