**Supplementary**

**Figure S1: Evaluation of the risk of bias of included studies**

**Table S1: Meta-regression analysis of the efficacy of fixed-ratio combination treatment and baseline characteristics**

**Table S2: Dosages of insulin and GLP-1 in the fixed-ratio combination treatment**

**Table S1: Meta-regression analysis of the efficacy of fixed-ratio combination treatment and baseline characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| Variables  | ß | 95%CI | P value |
| Total group |  |  |  |
| HbA1c changes from baseline |  |  |  |
| Age  | 0.115 | -4.357,4.587 | 0.799 |
| Sex  | -0.074 | 0.743,0.596 | 0.396 |
| BMI | 0.575 | -3.002,4.153 | 0.290 |
| HbA1c | -0.782 | -16.095,14.530 | 0.633 |
| Duration of diabetes | 0.076 | -1.943,2.096 | 0.715 |
| Weight  | -0.058 | -0.935,0.819 | 0.557 |
| Dosage of insulin | 0.103 | -1.533,1.738 | 0.571 |
| Weight changes from baseline | -0.045 | -1.972,1.882 | 0.817 |
| FPG changes from baseline |  |  |  |
| Age  | -0.708 | -12.189,10.774 | 0.577 |
| Sex  | -0.072 | -3.048,2.903 | 0.809 |
| BMI | 4.916 | -5.990,15.823 | 0.110 |
| HbA1c | -5.137 | -48.071,37.797 | 0.370 |
| Duration of diabetes | 1.000 | -4.271,6.270 | 0.250 |
| Weight  | -1.350 | -4.142,1.442 | 0.103 |
| Dosage of insulin | 0.579 | -10.110,11.270 | 0.616 |
| Weight changes from baseline | -0.176 | -8.698,8.346 | 0.837 |
| Weight changes from baseline |  |  |  |
| Age  | -0.234 | -16.505,16.038 | 0.885 |
| Sex  | 0.109 | -2.344,2.561 | 0.673 |
| BMI | -2.227 | -23.053,18.600 | 0.404 |
| HbA1c | -4.072 | -78.189,70.044 | 0.612 |
| Duration of diabetes | 0.128 | -8.560,8.817 | 0.882 |
| Weight  | 0.522 | -4.651,5.694 | 0.422 |
| Dosage of insulin | -0.512 | -3.437,2.412 | 0.529 |
| IGlarLixi group |  |  |  |
| HbA1c changes from baseline |  |  |  |
| Age  | 0.278 | -0.500,1.055 | 0.138 |
| Sex  | -0.157 | -0.668,0.354 | 0.159 |
| BMI | -0.746 | -5.042,3.550 | 0.271 |
| HbA1c\* | / | / | / |
| Duration of diabetes | 0.133 | -0.188,0.454 | 0.119 |
| Weight  | -0.296 | -0.780,0.187 | 0.081 |
| Dosage of insulin | 0.070 | -0.045,0.185 | 0.081 |
| Weight changes from baseline | 0.243 | -12.025,12.511 | 0.843 |
| FPG changes from baseline |  |  |  |
| Age  | 1.116 | -7.476,9.709 | 0.347 |
| Sex  | -0.628 | -5.836,4.581 | 0.368 |
| BMI | -2.789 | -36.303,30.725 | 0.482 |
| HbA1c\* | / | / | / |
| Duration of diabetes | 0.538 | -3.330,4.405 | 0.328 |
| Weight  | -1.359 | -7.205,4.488 | 0.208 |
| Dosage of insulin | 0.300 | -1.332,1.931 | 0.258 |
| Weight changes from baseline | -0.442 | -60.275,59.392 | 0.940 |
| PPG changes from baseline |  |  |  |
| Age  | -0.262 | -8.176,7.653 | 0.747 |
| Sex  | 0.162 | -4.325,4.650 | 0.726 |
| BMI | 1.150 | -19.834,22.134 | 0.613 |
| HbA1c\* | / | / | / |
| Duration of diabetes | -0.115 | -3.900,3.669 | 0.765 |
| Weight  | 0.134 | -9.015,9.283 | 0.883 |
| Dosage of insulin | -0.043 | -2.098,2.012 | 0.834 |
| Weight changes from baseline | -2.457 | -10.335,5.421 | 0.157 |
| Weight changes from baseline |  |  |  |
| Age  | 0.052 | -3.178,3.283 | 0.871 |
| Sex  | -0.035 | -1.894,1.824 | 0.851 |
| BMI | -0.314 | -9.798,9.169 | 0.746 |
| HbA1c\* | / | / | / |
| Duration of diabetes | 0.021 | -1.504,1.547 | 0.888 |
| Weight  | -0.001 | -3.426,3.423 | 0.997 |
| Dosage of insulin | 0.005 | -0.787,0.797 | 0.952 |
| IDegLira group |  |  |  |
| HbA1c changes from baseline |  |  |  |
| Age  | 0.108 | -0.231,0.447 | 0.385 |
| Sex  | -0.033 | -0.146,0.080 | 0.421 |
| BMI | -0.077 | -0.345,0.191 | 0.426 |
| HbA1c | -0.531 | -1.942,0.880 | 0.317 |
| Duration of diabetes | 0.063 | -0.231,0.357 | 0.543 |
| Weight  | -0.019 | -0.091,0.053 | 0.457 |
| Dosage of insulin | -0.031 | -0.132,0.070 | 0.402 |
| Weight changes from baseline | 0.118 | -0.194,0.431 | 0.314 |
| FPG changes from baseline |  |  |  |
| Age  | 0.232 | -1.602,2.066 | 0.714 |
| Sex  | -0.088 | -1.117,0.940 | 0.802 |
| BMI | -0.146 | -2.065,1.773 | 0.825 |
| HbA1c | -0.685 | -6.803,5.461 | 0.746 |
| Duration of diabetes | 0.057 | -1.545,1.658 | 0.918 |
| Weight  | -0.036 | -0.590,0.518 | 0.849 |
| Dosage of insulin | -0.042 | -0.475,0.391 | 0.778 |
| Weight changes from baseline | 0.126 | -1.128,1.380 | 0.770 |
| Weight changes from baseline |  |  |  |
| Age  | 0.263 | -13.406,13.932 | 0.848 |
| Sex  | -0.522 | -8.581,7.538 | 0.562 |
| BMI | 0.220 | -20.633,21.072 | 0.915 |
| HbA1c | -4.572 | -61.893,52.748 | 0.496 |
| Duration of diabetes | -0.073 | -13.120,12.973 | 0.954 |
| Weight  | 0.064 | -4.494,4.823 | 0.891 |
| Dosage of insulin | -0.058 | -3.011,2.894 | 0.843 |

**\*** HbA1c dropped from the model because of the collinearity.

**Figure S1: Evaluation of the risk of bias of included studies**



**Table S2: Dosages of insulin and GLP-1RA in the fixed-ratio combination treatment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Authors  | Treatment | Dosage of insulin(u) | Dosage of GLP-1RA | Titration recommendations |
| IGlarLixi |  |
| Rosenstock 2016-1 | IGlarLixi | 36 | 18 ug | The initial daily dose was 10 units Gla100/5 mg lixisenatide in the LixiLan group and 10 units in the Gla-100 group. The titration of Gla-100 (alone and in the LixiLan combination) was based on plasma glucose levels; plasma glucose was measured, and corresponding dose changes were made to allow patients to achieve FPG targets of 4.4– 5.6 mmol/L. For LixiLan, the dose of lixisenatide followed the Gla100 dose according to the 2 units/1 mg ﬁxed ratio. The maximum daily dose for LixiLan was 60 units Gla-100 corresponding to 30 mg lixisenatide.  |
| IGlargine | 39 |  | No upper limit of titration was set for the Gla-100 group. |
| Rosenstock, 2016 | IGlarLixi | 39.86±14.9 | ~20 ug | Treatment was titrated once a week to reach and maintain a self-measured FPG of 80– 100mg/dL while avoiding hypoglycemia. Titration for iGlarLixi and iGlar by only 2–4 units weekly was similarly guided only by the required dose for iGlar on the basis of the following algorithm: +2 units (if FPG was >100 and ≦140mg/dL) or +4 units (if FPG was >140 mg/dL). |
| IGlargine | 40.36±14.9 |  | The titration regimen was the same as with iGlarLixi. |
|  | Lixisenatide |  | 20ug | Lixi was supplied in disposable preﬁlled pens containing 50 mg/mL for the starting dose of 10 mg for the ﬁrst 2 weeks and a different pen containing 100 mg/mL for the 20 mg maintenance dose during the remainder of the study. |
| Aroda, 2016 | IGlarLixi | 46.7±12.6 | ~17ug | The starting dose was kept stable for 2 weeks, with subsequent titration once a week to reach and maintain a target fasting SMPG of 80–100 mg/dL while avoiding hypoglycemia. Titration of iGlarLixi was based on the required dose of iGlar according to the following algorithm: +2 units (if FPG was >100 and ≦140 mg/dL) or +4 units (if FPG was >140 mg/dL). |
| IGlargine | 46.7±12.7 |  | The titration regimen was the same as with iGlarLixi. |
| IDegLira |  |
| Rodbard, 2016 | IDegLira | 28 | 1.0 mg | Doses of IDegLira or placebo were adjusted twice per week according to a predeﬁned titration algorithm, based on the mean fasting prebreakfast self-monitored blood glucose (SMBG) measurements, from 3 consecutive days, aiming to achieve a mean pre-breakfast blood glucose concentration of 4.0–6.0 mmol/l. The maximum allowed doses were 50 dose steps for IDegLira (50 U insulin degludec and 1.8 mg liraglutide) and 50 dose steps of placebo. |
| Placebo |  |  |
| Linjawi, 2015 | IDegLira | 43 | 1.55 mg | Based on the three preceding pre-breakfast SMBG measurements, IDegLira was itrated twice a week to a FPG target 4.0–6.0 mmol/l. The maximum allowed doses were 50 dose steps for IDegLira. |
| Lingvay, 2016 | IDegLira | 41 | 1.48 mg | The maximum allowed dose was 50 dose steps providing 50U of degludec and 1.8mg of liraglutide.In both groups, target-driven titration was performed twice weekly based on the mean of 3 previous daily self-monitored prebreakfast blood glucose measurements. If this mean was above or below the 72 to 90mg/dL target, patients were to respectively increase or decrease the dose by 2 dose steps or 2U. |
| IGlargine | 66 |  | Patients randomized to glargine continued treatment with their pretrial dosing,with no maximum daily dose during the trial period. |
| Gough, 2014 | IDegLira | 38±13 | 1.4±0.5 mg | IDegLira was started at 10 dose steps (10 U insulin degludec plus 0·36 mg liraglutide, once daily). On the basis of prebreakfast self-monitored blood glucose measurements (mean from three consecutive days), doses of IDegLira and insulin degludec were titrated individually twice per week to achieve a prebreakfast plasma glucose of 4–5 mmol/L by use of an algorithm. The daily dose of IDegLira could be titrated to 50 dose steps (50 U insulin degludec plus 1·8 mg liraglutide). |
| IDegludec | 53±28 |  | The starting dose of insulin degludec alone was 10 U once daily, no maximum dose was speciﬁed for insulin degludec alone. |
| Liraglutide |  | 1.8±0.5 mg | Liraglutide was started at 0·6 mg per day and was increased by 0·6 mg per week to a maximum of 1·8 mg per day. |
| Buse, 2014 | IDegLira | 45 | 1.62 mg | Doses of IDeg and IDegLira were adjusted biweekly according to a predeﬁned titration algorithm, based on selfmeasured prebreakfast FPG (mean of 3 consecutive days), striving for a mean prebreakfast glucose concentration of 4.0–5.0 mmol/L. Maximum dose was 50 units IDeg or 50 dose steps IDegLira (50 units IDeg plus 1.8 mg liraglutide). |
| IDegludec | 45 |  |