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(RESEARCH ARTICLE)

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Comparison of adverse effects among different GLP-1 receptor agonists added to basal insulin, and between GLP-1 receptor agonists and basal insulin versus Basal-plus or basal-bolus insulin in type 2 diabetes: A meta-analysis

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Abstract

Diabetes mellitus type 2/ DM2/ - is increasing in incidence in United states and throughout the world mostly due to increasing Obesity epidemy- around 40 % of adult people in USA. Two are the major defects of the disease- insulin resistance which sets up the stage 4-7 years before DM type 2 is diagnosed and relative to the increased resistance insulin deficiency. After the diagnosis of DM type 2 the Insulin resistance stays usually constant while the Insulin deficiency progresses necessitating the intensification of the therapy and eventually the need of Insulin . Initially the insulin is started usually as a basal and eventually as the DM type 2- progresses we add bolus rapid acting insulin to major meal- basal plus regimen/BP/ and eventually to every meal- basal- bolus /BB/ insulin. This intensification of the therapy is frequently able to control DM type 2 , but leads to significant 3-4 kg weight gain with risk of hypoglycemia.

Other option of intensification of the therapy of DM type 2 is to add to the oral anti - diabetic medications only basal Insulin and GLP1- RAs. GLP1-RAs decrease post prandial blood sugar as the rapid acting insulin does and the long acting GLP1-RAs also decrease fasting blood sugar. GLP1- RAs suppress the appetite and theoretically might lead to weight loss and less incidence of hypoglycemia compare to BP/BB Insulin regimens, because they act on glucose dependent manner- increase the endogenous insulin production only if the blood sugar is elevated .

In our meta- analysis we concentrated our efforts into looking at the side effect of GLP 1- RAs and basal- Insulin combination compare to BP/BB insulin combination like weight loss/gain, incidence of hypoglycemia, adverse events- mainly the gastrointestinal ones.

Our secondary end point was the change in HbA1c between GLP1-RAs and basal insulin group compare to BP/BB insulin group in patients with HbA1c 7-11%.

This is the first meta- analysis as far as we now comparing those 2- combinations – BB/BP insulin to GLP1-RAs and basal insulin in the terms of looking as a primary end point at the side effects of those combinations.

Keywords: Basal Insulin; Bolus Insulin; GLP1-Receptor agonists-GLP1-RAs; Diabetes Mellitus type 2-DM2; Hypoglycemia; Weight gain

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1. Introduction

Type 2 diabetes treatment and management continues to be a mainstay of medical care in the United States. It was estimated in 2018 that approximately 34- million Americans have type 2 diabetes, and 100 - millions have pre- Diabetes mellitus type 2 therefore physicians from various specialties will encounter diabetic patients and be required to make appropriate management decisions [1]. It is estimated by 2060 that there will be a total of nearly 60 million adult diabetics in the United States. [2].Diabetes is the major cause of blindness, kidney failure, stroke, heart attack and lower extremities amputation. This is leading to a major impact on people with diabetes and their families as well economic impact on the health-care system [1-2].

If the glycemic targets are not reached, current guidelines for treatment of Diabetes Mellitus type 2/DM2/ recommend dual-agent therapy, followed by triple-agent therapy. More complex regimens include adding basal Insulin agents or basal-plus rapid acting insulin agent before the largest meal of the day /BP/ and Basal-Bolus Insulin therapy- basal plus 3- injections of rapid acting insulin agent before each meal /BB/. However, despite the polytherapy, many patients are still not reaching their HbA1c targets.

Glucagon-like peptide receptor 1 agonists (GLP1- RAs) are a relatively new medication used to treat type 2 diabetes in the last 15- years. Currently there are several different forms including short acting, long acting GLP1-RAs, and fixed ratio combinations with basal insulin.

The short acting ones are exenatide and lixisenatide and the long-acting ones are dulaglutide, albiglutide, exenatide, long-acting release semaglutide and Liraglutide. The fixed GLP1-RAs and Basal Insulin combinations are IDegLira and iGlarLixi. They are typically administered as an injection (frequency varies depending on duration of action), however oral administrations of Semaglutide also exists though less commonly prescribed due to cost and insurance issues.

GLP1- RAs have been shown to have a cardiovascular benefit, renal benefit and have been shown to effectively lower hemoglobin A1c levels in type two diabetic patients. [3-5].The GLP-1 RAs act by stimulating Insulin secretion from the pancreas in Glucose dependent manner and suppress glucagon secretion from the pancreatic alfa cells and glucose output from the liver, while also promoting satiety through central mechanisms and slow the gastric emptying.

Long acting GLP1- RAs are more effective than short ones in lowering the HbA1c. The short acting GLP1 -RAs decrease post- prandial glucose excursions and gastric emptying while long acting GLP1- RAs reduce both fasting and postprandial glucose excursions. Those drugs have low incidence of causing hypoglycemia as well.

Current guidelines recommend that antihyperglycemic treatment in patients with type 2 diabetes not adequately controlled on basal insulin should be intensified by adding GLP1-RAs or starting BP/BB insulin therapy.

There are limitations with these medications, as they cannot be used in patients with a history of multiple endocrine neoplasia type 2 or personal or family history of medullary thyroid cancer, and caution should be used if there is a history of pancreatitis. GLP1- RAs are frequently associated with adverse effects such as gastrointestinal disturbance. This side effect, and the requirement of frequent injections can be a reason for the lack of compliance [6].

In this study we performed a meta- analysis of randomized clinical trials (RCTs) in which GLP1- RAs were used in combination with basal insulin and compare this therapy to insulin therapy alone as BP/BB insulin used to intensify the treatment of DM type 2.

The focus of our meta-analysis was to look at difference of hypoglycemia, body weight change and GI adverse events as a primary outcome of our study. The secondary outcome of our study was the change in HbA1c. We looked at the randomized control trials in which GLP1- RAs were added to Basal insulin versus when the intensification of the treatment was done by using BP/BB Insulin. Importantly we looked at the adverse events and effect of the different GLP1 -RAs when added to basal insulin as well as the overall difference between GLP1-RAs added to basal insulin as a group versus BP/BB insulin group.

This was the main difference in our study compare to other studies.

2. Material and methods

2.1. Study Question

Primary endpoint of our meta-analysis was to compare the effect of different GLP1-RAs added to basal insulin as well as overall as a group GLP1-RAs added to basal insulin versus basal- plus insulin or basal-bolus insulin used for intensification of treatment of decompensated type-2 DM with HbA1c between 7-11% on incidence of hypoglycemia, body weight or incidence of GI adverse events. The secondary outcome in our study was the difference in both regimens on the change of HbA1c.

2.2. Search Strategy

PubMed search for RCTs was performed from data-base inception to January 21, 2021. The following keywords/search terms were used: GLP-1, GLP-1 receptor agonist, basal insulin, basal plus insulin/BP/, basal bolus insulin/BB/, HbA1c, weight loss, hypoglycemia, and GI adverse events. A manual search was also performed using reference lists from prior meta-analyses. [7-11] RCTs were included in the study if the study population included participants with baseline A1C > 7% to 11 %, if above mentioned parameters in the study question were included in study outcomes, and if a comparison of patients taking GLP1-RAs and basal insulin versus basal- plus and/or basal-bolus insulin was performed. 3- Investigators/ A. M., A.H. and K. L. / independently searched papers, screened titles, and abstracts of the retrieved articles, reviewed full text articles and selected articles for their inclusion. No language restriction was adopted.

2.3. Study Selection and Data Extraction

The studies were reviewed and screened by three investigators and selected if deemed appropriate. The following information was extracted independently by the same investigators:

General information on the study- author, year of publication, study name, study type, number of patients age, diabetes duration, glucose lowering medications, treatment of randomization, and [2] end points including body weight, incidence of hypoglycemia, GI adverse events, change in HbA1c.

The studies were then stratified based on the type of GLP1-RAs/ short versus long acting/ and placed into the following subgroups: exenatide and basal insulin versus basal-plus/basal-bolus insulin, lixisenatide and basal insulin versus basal-plus/basal-bolus insulin, liraglutide and basal insulin versus basal-plus /basal-bolus insulin, albiglutide and basal insulin versus basal-plus /basal-bolus insulin, dulaglutide and basal insulin versus basal-plus or basal-bolus insulin, and insulin degludec and liraglutide fixed dose ratio combination versus basal-plus /basal-bolus insulin and also analysis of the between different GLP1-RAs plus basal insulin was conducted. These studies were then sent to a fourth researcher for confirmation of meeting the inclusion criteria and for extraction of the 95% confidence interval for GI adverse effects, body weight, and incidence of hypoglycemia and change of HbA1c between the groups [12-28].

2.4. Study Quality Assessment

The risk of bias of included studies was assessed independently by two reviewers/A.H and A.M. / through the Cochrane Collaboration's tool for assessing risk of bias for the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selecting reporting. Each domain was assigned low, unclear, or high risk of bias[29-30].

2.5. Statistical Analysis of the Data

Subgroup analysis was performed for GLP1- RAs and Basal Insulin in comparison to basal-bolus/basal-plus insulin and between the different GLP1- RAs for the primary outcomes including the change in the body weight, incidence of hypoglycemia and GI-adverse events adverse and secondary outcome- change in HbA1c. The mean difference (MD) was calculated for each subgroup with 95% confidence interval (CI) and placed in a Forest plot [Table 1, Table 2, Table 3, and Table 4].

2.6. Applicability of the Data

We believe that our data analysis is sufficient to be made recommendations for treatment of diabetes mellitus type 2 which needs intensification which strategy to be used - adding to basal insulin GLP1 -RAs versus using BP/BB strategy based on effect on body weight, incidence of hypoglycemia, GI adverse events and magnitude of reduction of HbA1C.

Table 1a Adverse Events comparison between different Different GLP1-RAs

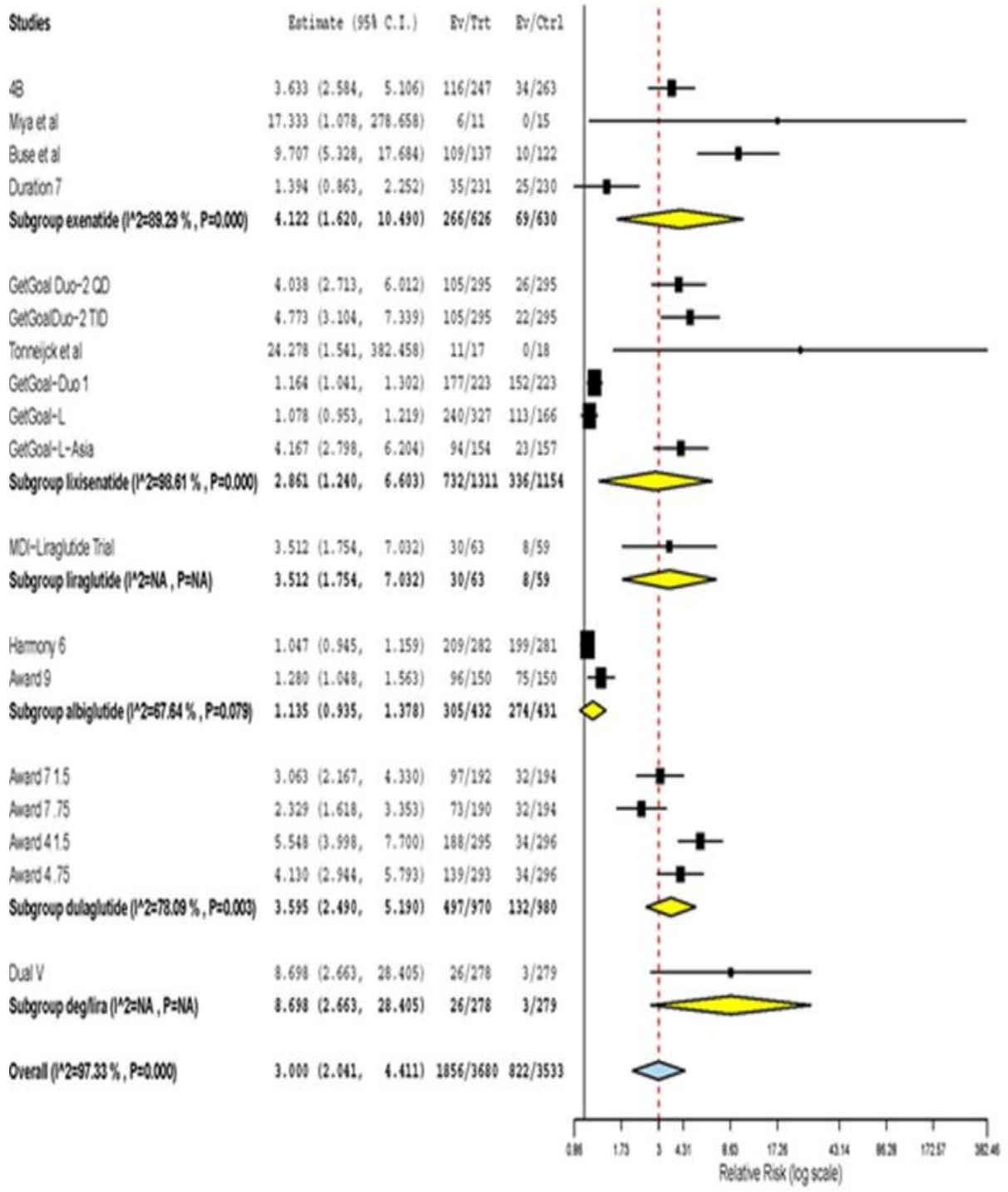


Table 1b Adverse events comparison between GLP1-RAs and basal insulin versus BP/BB insulin

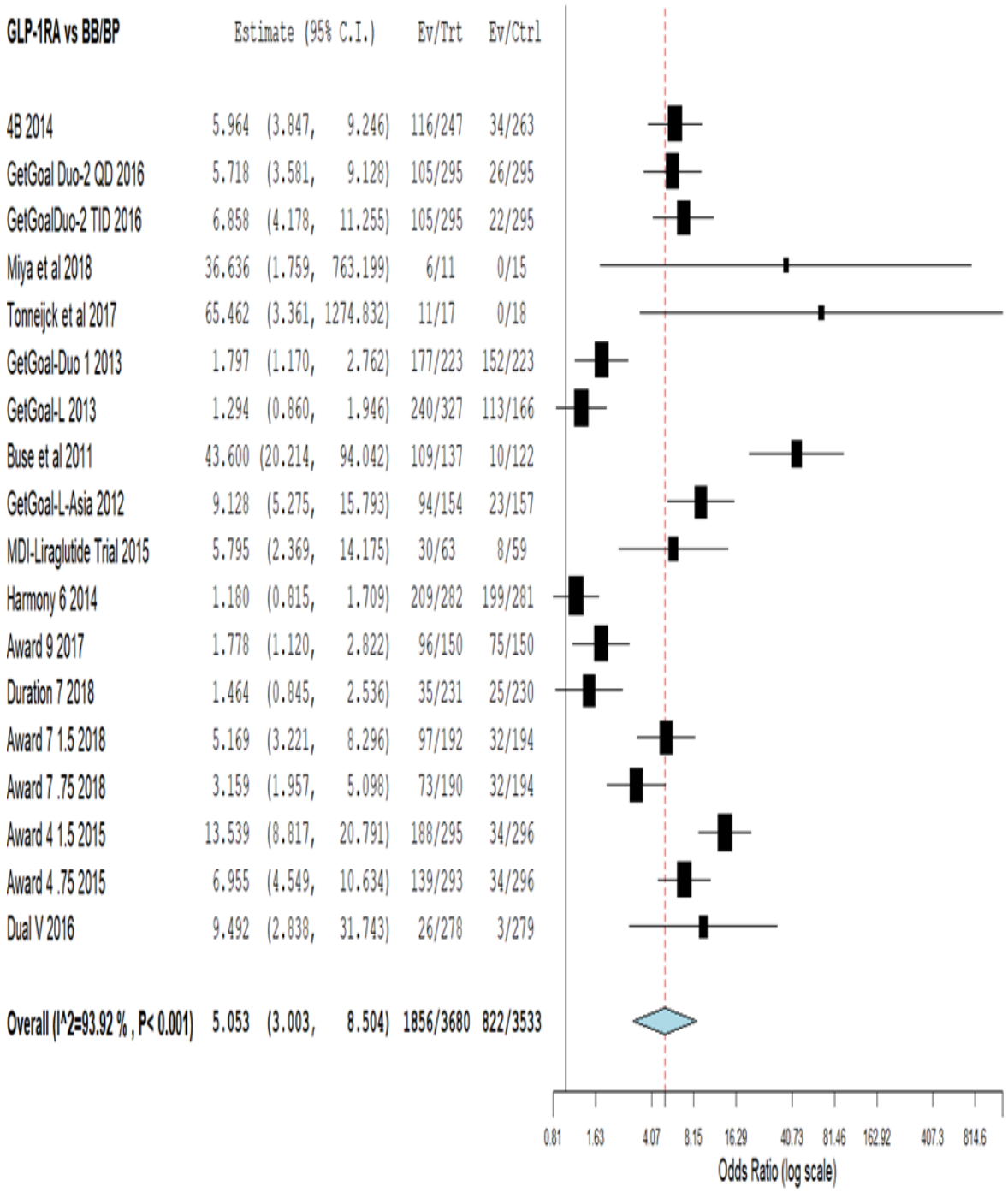


Table 2a Comparison of Hypoglycemia between different GLP1-RAs and basal Insulin

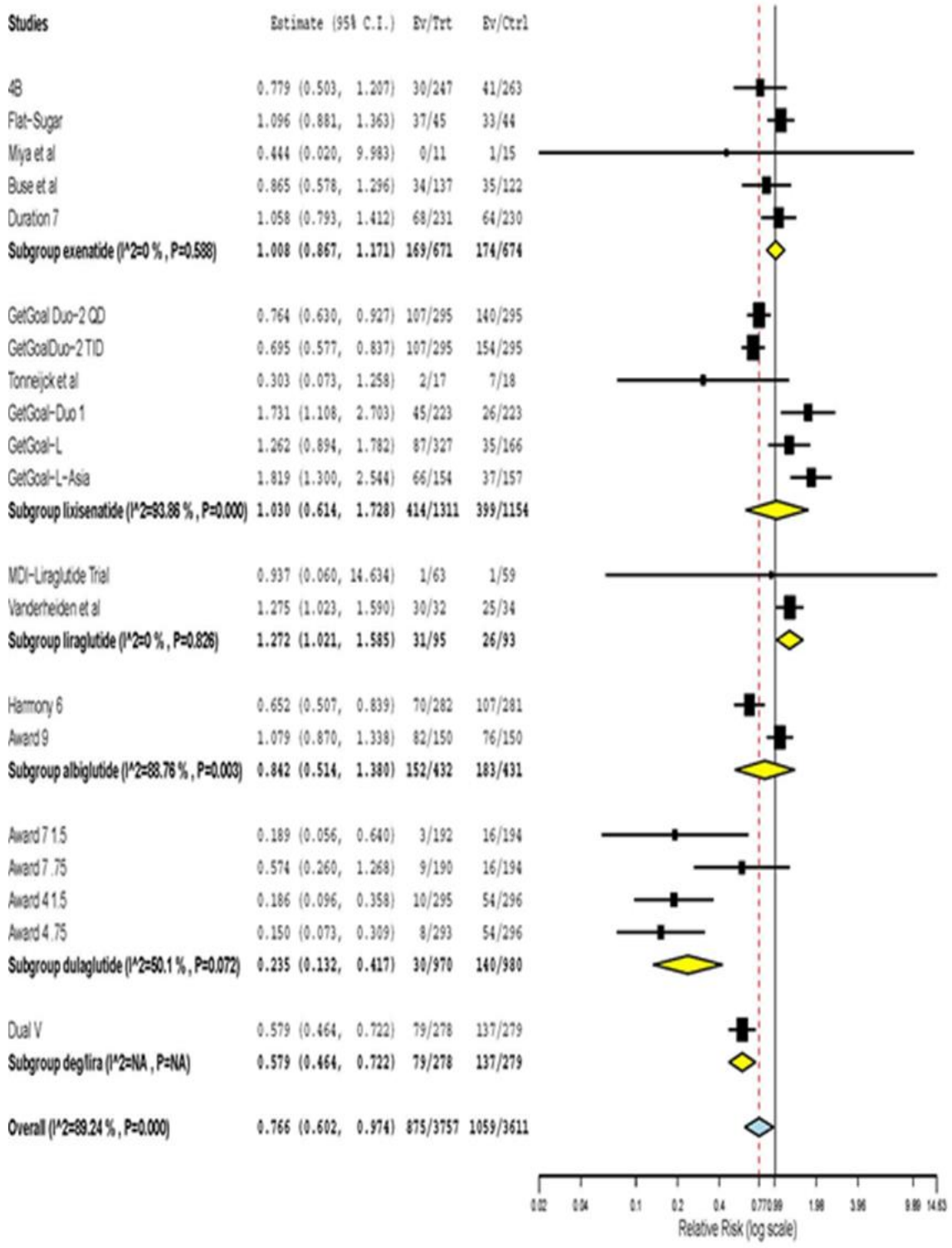


Table 2b Comparison of hypoglycemia between GLP1-RAs and basal insulin versus BP/BB insulin

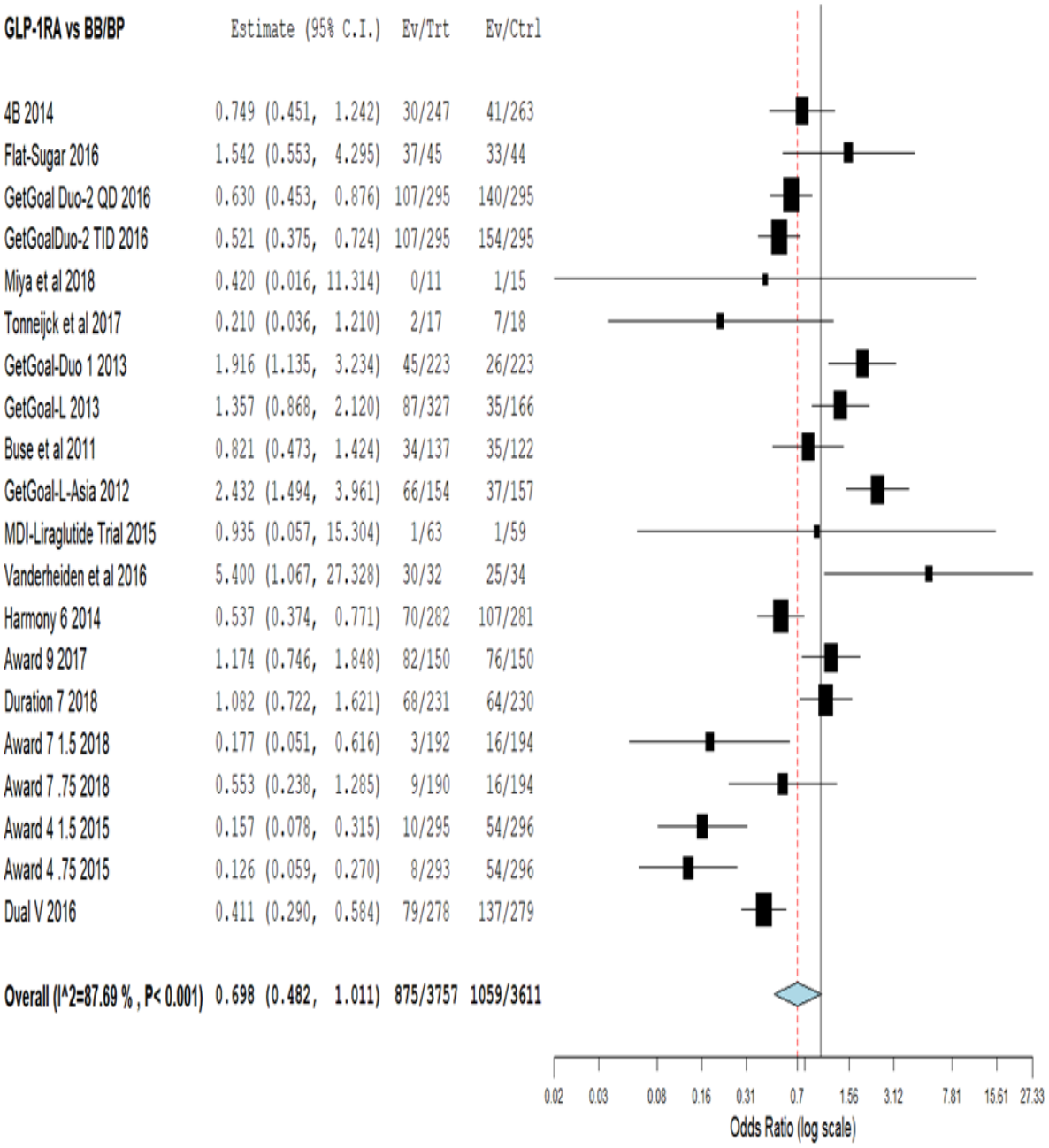


Table 3a Comparison in Change of HbA1c between different GLP1-RAs and basal insulin

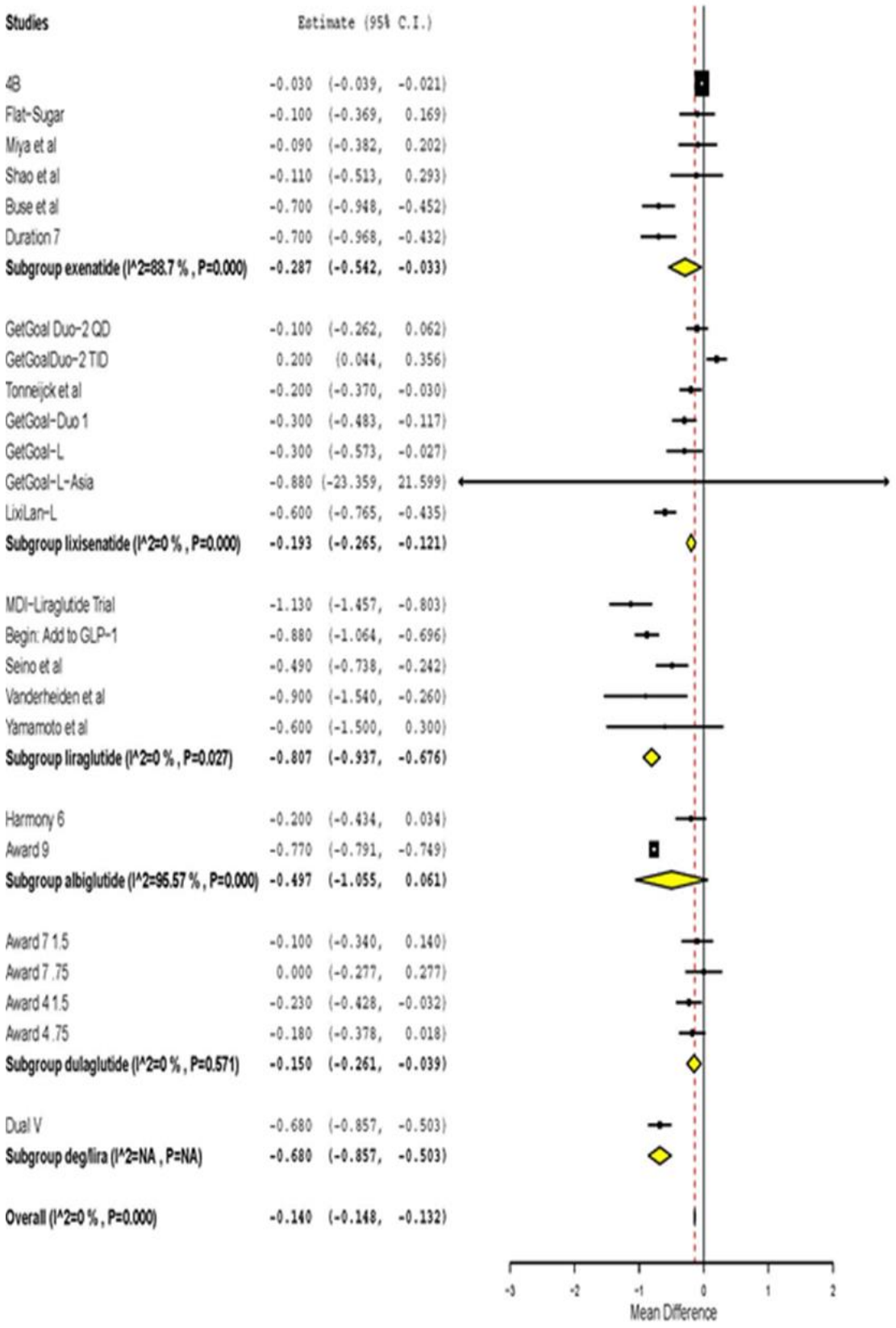


Table 3b Comparison in Change of HbA1c Between GLP1- RAs and basal Insulin compared to BP/BB Insulin

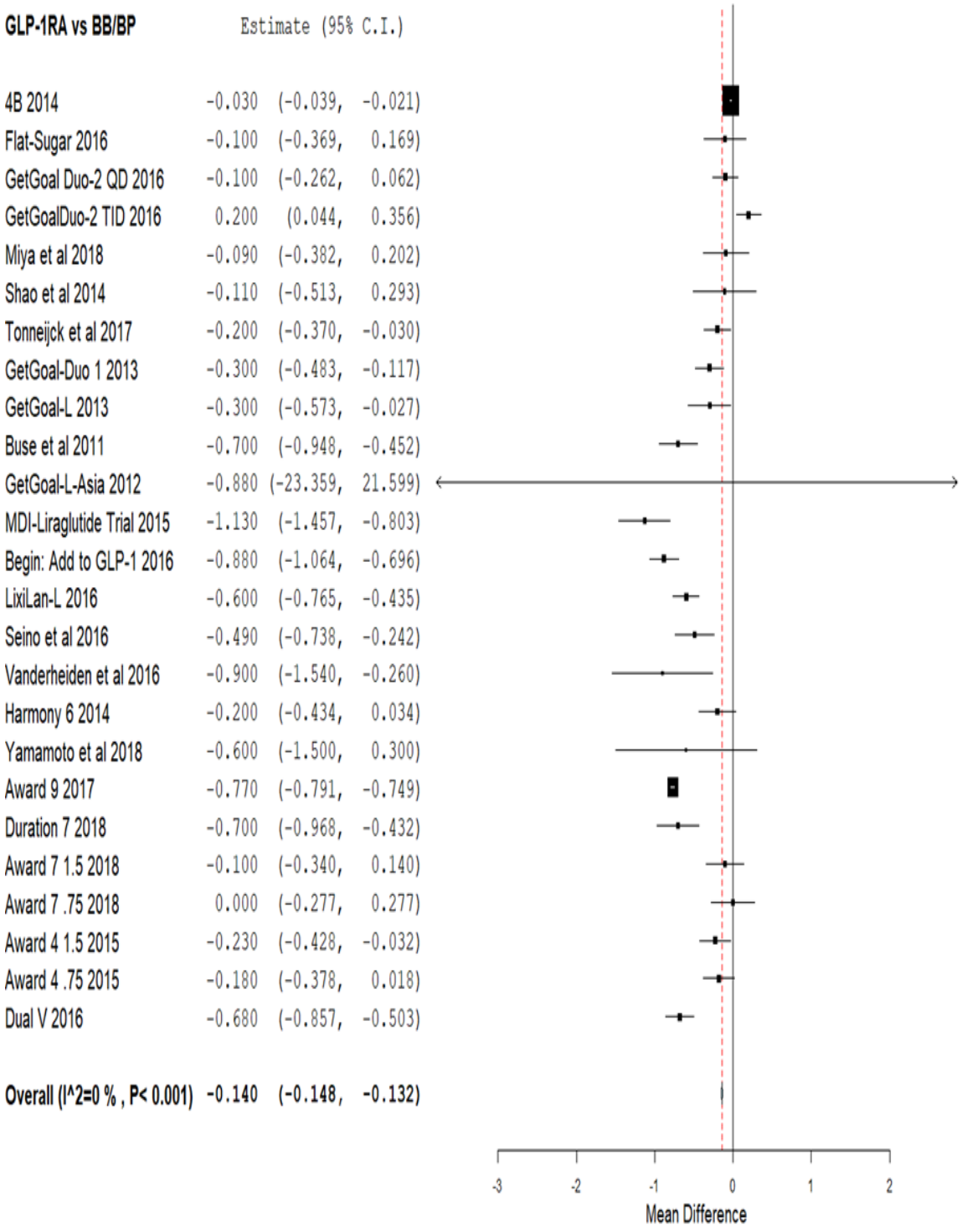


Table 4a Comparison in the Change in weight between Different GLP1-RAs and basal insulin

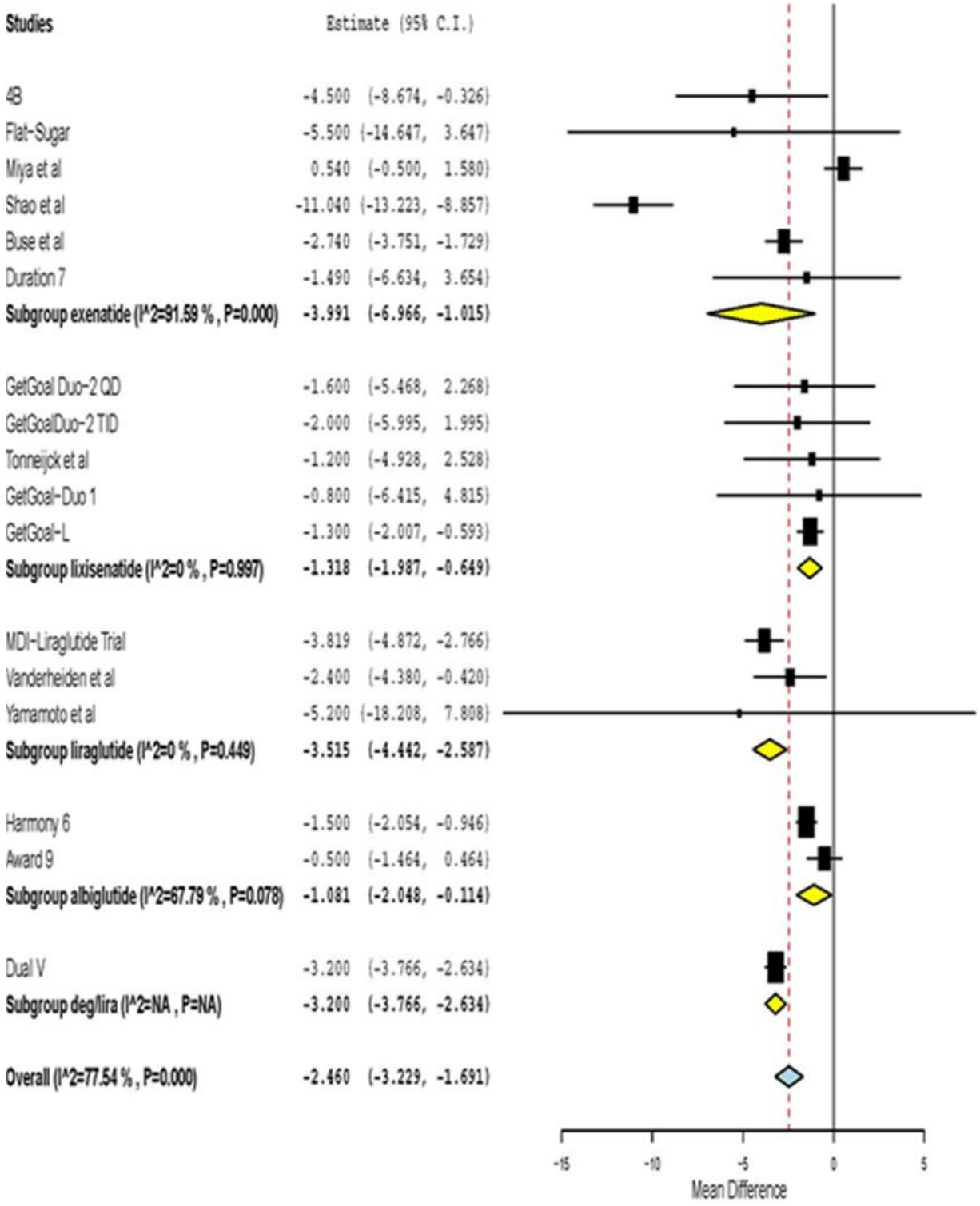
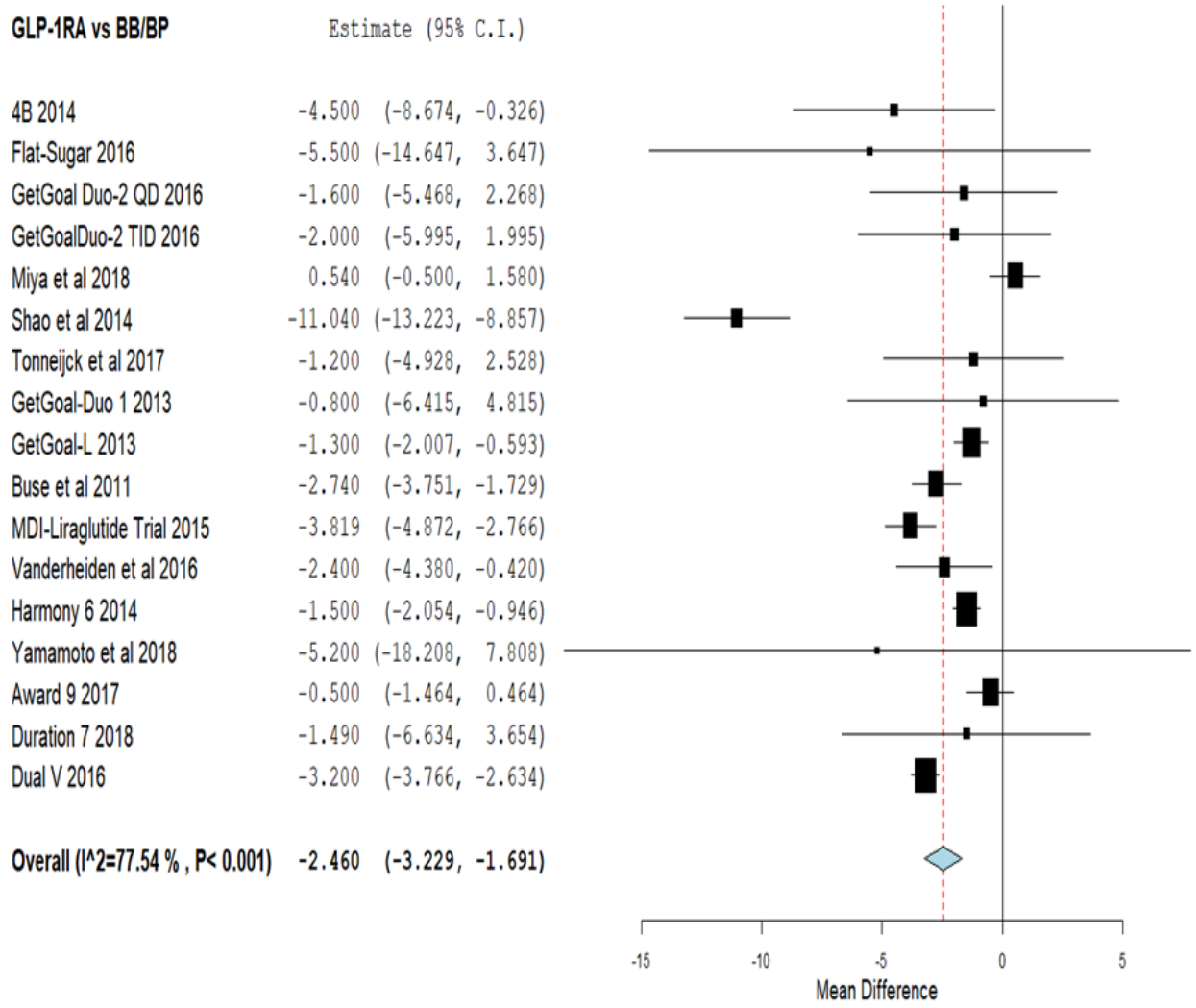


Table 4b Comparison of the change in weight between GLP1-RAs and basal insulin and BP/BB insulin



3. Results

The short acting GLP1-1RAs were included: exenatide and lixisenatide. The long-acting GLP1-RAs were included: liraglutide, albiglutide, and dulaglutide. A fixed ratio combination insulin degludec/liraglutide(IDegLira) was also included.

A total of 18 RCTs were found to meet our inclusion criteria for analysis of Gastrointestinal/GI/ adverse events (12-26). Among the short acting GLP1-RAs, exenatide added to Basal- Insulin was associated with more GI adverse effects (MD 4.122, 95% CI [1.620, 10.490], p = 0).

Among the long acting GLP-1RAs, dulaglutide was associated with more GI adverse effects (MD 3.595, 95% CI [2.490, 5.190], p = 0.003) when added to basal Insulin, however liraglutide also demonstrated a similar association with the adverse events (MD 3.512, 95% CI [1.754, 7.032], p = NA).

Overall, the fixed ratio combination insulin degludec/liraglutide regimen/IDegLira/ had the highest association with GI adverse effects (MD 8.698, 95% CI [2.663, 28.405], p = NA).

The combination of GLP1- RAs plus basal Insulin overall 5 times higher incidence of adverse events most of which were GI adverse events than BP/BP Insulin-(Odds ratio- 5.53, 95% CI [3.003, 8.504], P<0.001).

A total of 20 RCTs were found to meet the inclusion criteria for analysis of incidence of hypoglycemia (12-28).

Subgroup analysis for incidence of hypoglycemia was similar between the short acting GLP-1RAs; exenatide (MD 1.008, 95% CI [0.867, 1.171], p = 0.588) and lixisenatide (MD 1.030, 95% CI [0.614, 1.728], p = 0) added to basal Insulin not been able to be explained by the dose of the basal-insulin.

Liraglutide had the highest association with hypoglycemia (MD 1.272, 95% CI [1.021, 1.585], p = 0.826) amongst the long acting GLP-1RAs and overall, when added to basal- insulin which although was not significant and has not been able to be explained by the dose of the basal-insulin which was similar.

GLP1-RAs plus Basal Insulin overall had 31% lower incidence of hypoglycemia than BP/BB insulin regimens –(Odds ratio- 0.698, 95% CI [0.482,1.011], P<0.001).

A total of 17 RCTs (Table 4) were found to meet the inclusion criteria for analysis of change in body weight (12-19, 21-22, 26-28, 33).

Subgroup analysis found exenatide added to basal insulin (MD-3.2, 95% CI, [-3.766, -2.66] P-NA) to be the most effective for weight loss and this was statistically significant (MD -3.991, 95% CI [-6.966, -1.015], p = 0).

The other most effective regimens were Liraglutide added to Basal Insulin (MD -3.5, 95% CI [-4.442, -2.587] p-0.0.449) as well as the combination drug IDegLira (MD -3.2, 95% CI, [-3.766,-2.66] P-NA. All other regimens using combination of GLP1- RAs and Basal Insulin regimens were found to increase weight loss, however none were statistically significant.

The weight loss between GLP 1-RAs added to Basal Insulin overall was higher than BP/BB Insulin Groups (MD-2.460, 95% CI [-3.229,-1.691], P<0.001).

A total of 25 RCTs (Table 3) were found to meet the inclusion criteria for analysis of change in HbA1c. (12-28) Subgroup analysis found liraglutide added to basal insulin and basal-bolus insulin combination to be the most effective regimens for decreasing HbA1c (MD -0.807, 95% CI [-0.937, -0.676], p = 0.027.

The GLP1-RAs added to basal Insulin overall compare to BP/BB Insulin was found to statistically significantly decrease the HbA1c although the difference was very small (MD-0.140, 95% CI [-0.148,-0.132], p<0.001).

4. Discussion

The goal of systematic reviews and meta- analysis is to identify the best available evidence about the safety and efficacy of combination therapy among GLP1-RAs and basal Insulin as well as between GLP1-RAs and basal insulin versus BP/BB Insulin.

In our meta- analysis the main question to be answered compared to other meta – analysis was to look for the side effects like weight gain/weight loss, incidence of hypoglycemia or GI side effects among GLP 1 -RAs added to basal insulin. The second main primary outcome was to look at the side effects mentioned above with GLP1-RAs added to basal Insulin compare to BP/BB Insulin regimen.

The efficacy measured by lowering the HbA1c of the above-mentioned combinations was a secondary end point which makes our meta- analysis particularly important. To our knowledge this is the first meta- analysis looking at the side effects inside the GLP1-RAs group – short and long acting added to basal Insulin and between GLP1-RAs added to basal Insulin and BP/BB Insulin.

The efficacy of the regimens described was explored in the past in other meta-analysis and this is why we made the change of assessing the change in HbA1c as a secondary endpoint in our meta-analysis.

We included base on the specific outcomes we looked at between 17 and 25 RCT- randomized controlled trials.

The main adverse event of some glucose- lowering medications is hypoglycemia and this can be minimized with the use of GLP1-RAs which act at glucose dependent manner. There was non- statistically significant difference among short and long acting GLP1-RAs when added to basal Insulin in the incidence of hypoglycemia which was 31% lower than BP/BB insulin regimens. This makes GLP1-RAs very attractive choice when added to basal Insulin rather than using BP/BB for intensification of treatment of patients with DM type 2 uncontrolled on their current regimens.

The DM type 2 is also associate with being overweight or obese exacerbating morbidity and mortality due to vascular disease. Current guidelines recommend weight loss 5-10% in these patients since the weight loss is associated with improved glycemic control. BP/BB Insulin regimens are associated with weight gain 4.3 +/- 2.7 kg in different studies in the past. In our study GLP1-RAs added to Basal Insulin promoted weight loss which was non-significantly higher when Liraglutide was added to basal insulin and combination IdegLira. The patients lost 2.46 kg overall versus BP/BB Insulin regimens. This is another reason to choose the combination between GLP1-RAs and basal insulin to BP/BB while treating uncontrolled DM type 2.

In our meta-analysis GLP1-RAs plus basal Insulin overall decreased significantly more HbA1c than BP/BB Insulin overall although the difference was very small- minus 0.140% in patients with HbA1c between 7-11%. Liraglutide when added to basal insulin was the most successful combination in lowering HbA1c.

This similar to slightly better lowering of HbA1c when GLP1-RAs was added to basal insulin compare to BP/BB Insulin was confirmed in other meta-analysis and this why we concentrated our efforts in looking at the adverse events which favor GLP1-RAs and basal Insulin versus BP/BB Insulin.

We need to acknowledge the higher incidence of Adverse events mostly GI side effects which we have found in our meta-analysis when the GLP1-RAs is added to Basal Insulin compare to BP/BB insulin.

5. Limitations

Several studies did not specify gastrointestinal /GI/ adverse events, counting total adverse events since most patients experienced gastrointestinal related adverse events. However, this could overestimate adverse GI events in some studies.

Only one study was included in the fixed dose combination GLP-1RA and insulin study arm, and only one study was included in the subgroup analysis for adverse effects in the liraglutide.

Also, there was high heterogeneity of the studies which we used.

Further RCTs will be needed to obtain a more accurate assessment of these medication regimens.

6. Conclusion

In patient with type 2 diabetes mellitus a combination therapy with GLP1-RAs and basal Insulin lead to significant weight loss and lower incidence of hypoglycemia compare to Basal- plus or Basal- bolus insulin regimen, but higher incidence of GI related adverse events.

The GLP1-RAs plus basal insulin was in our meta- analysis as slightly more effective than BP/BB insulin combination in lowering the HbA1c.

Given the lower incidence of the adverse events particularly hypoglycemia and weight gain GLP1- RAs added to basal Insulin may be used preferentially or as alternative to BP/BB Insulin whenever patients with type 2 DM need intensification of their treatment.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest of the authors

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