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# Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: a systematic review

Running title: Predictors of efficacy of incretins

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**Abstract**

**Aims:** To identify the determinants of efficacy of glucagon-like peptide-1 receptor agonists (GLP-1A) and dipeptidyl peptidase-4 inhibitors (DPP-4I).

**Methods:** MEDLINE and EMBASE were searched between 01/01/2011 and 15/08/2014 for randomized controlled trials of 12 to 52 weeks' duration, which reported the change in glycated hemoglobin (HbA1c) from baseline as the primary end point, and reported data about predictors of efficacy of incretins.

**Results:** Among 4172 studies found, 77 studies reported data on baseline HbA1c, age, sex, ethnicity, body mass index (BMI), and history of diabetes in relation to change in HbA1c.

For DPP-4I, 37 out of 47 studies reported a greater decrease in HbA1c among patients with higher baseline HbA1c. Most DPP-4I studies reported no variation in efficacy in regard to demographic characteristics or BMI. Among 17 studies reporting on GLP-1A, baseline higher HbA1c was reported as predictive of a greater response in 7 out of 9 studies; 13 studies reported data about other factors, without consistent findings.

**Conclusions:** Current evidence suggests that higher baseline HbA1c is associated with a greater efficacy of both DPP-4I and GLP-1A therapies in lowering HbA1c. The roles of other potential predictors are less consistent across studies and require further investigation.

**Keywords:** diabetes, incretin therapy, efficacy, determinant factors

## Introduction

Incretin-based therapies, dipeptidyl peptidase-4 inhibitors (DPP-4I) and glucagon-like peptide-1 receptor agonists (GLP-1A) are relatively new antihyperglycaemic agents used in the treatment of diabetes. Currently, diabetes treatment guidelines recommend a patient-centered approach in treatment intensification strategies for type 2 diabetes [1]. Understanding predictors of response should be an important component of tailoring treatment for individuals. However, no guidelines to date described which individual parameters, such as age, gender, body mass index (BMI), or ethnicity can be used as reliable predictors of a response to these drugs [2].

Among the sparse data, two systematic reviews of predictors of response to DPP-4I treatment reported that higher baseline HbA1c was correlated with a greater decrease of HbA1c [3,4] while a third review reported the opposite, that higher HbA1c was associated with smaller reduction in HbA1c [5]. This leads to significant uncertainty in regard to the relationship between baseline HbA1c and subsequent HbA1c response to DPP-4I. It was also reported that higher fasting plasma glucose (FPG), FPG:HbA1c ratio and BMI were predictors of a lower response of DPP-4I, whereas older age or Asian ethnicity were associated with a greater efficacy [3,5]. In another meta-regression analysis, the baseline HbA1c, fasting glucose and the type of DPP-4I explained respectively 22 %, 19 % and 12 % of between-study variance; while the mean age of patients, length of treatment with a DPP-4I, the use of previous anti-diabetic drugs resulted in no further increment of explained variance [4]. No systematic reviews of predictors of response to GLP-1A have been published.

One of the key limitations of the available DPP-4I reviews is that they analysed study-level data, rather than individual-level data. Thus, these reviews relate mean baseline parameters to mean changes in HbA1c across multiple studies, an approach which carries a risk of

identifying biased or confounded results, and might explain the surprising conclusion that lower baseline HbA1c predicted a greater HbA1c response [5]. This limitation would be overcome by collating all the individual-participant data, but this is not currently possible. An alternative approach is to identify all the individual studies that report on possible predictors of efficacy, and to aggregate their reported findings. Since each of these analyses is based on individual-participant data, it should provide an important insight into the available information on predictors of change in HbA1c.

The aim of this review was to describe the available data on predictors of HbA1c response to incretin-based therapies, with a particular focus on the uncertainty in regard to the role of baseline HbA1c.

## **Materials and methods**

### ***Literature search***

A literature search of MEDLINE and EMBASE was performed from 1st January 2011 to 15th August 2014, using all of the following keywords for DPP-4I: dipeptidyl peptidase-4 inhibitor, dipeptidyl peptidase-IV inhibitor, DPP-4 inhibitor, DPP4 inhibitor, DPP-IV inhibitor, incretin mimetic, saxagliptin, sitagliptin, vildagliptin, alogliptin, linagliptin, dutogliptin, tenegliptin, gemigliptin ; and for GLP-1A : GLP-1 receptor agonist, GLP-1 mimetic, GLP-1 analogue, GLP-1 analog, glucagon-like peptide-1 receptor agonist, glucagon-like peptide-1 mimetic, glucagon-like peptide-1 analogue, glucagon-like peptide-1 analog, exenatide, exendin, liraglutide, taspoglutide, albiglutide, lixisenatide, albugon and dulaglutide. Searches were limited to clinical trials; for the Medline search, we restricted the search combining the following terms: clinical trial, controlled clinical trial, randomized

controlled trial, random\*, clinical trial\*, controlled trial\*. For Embase we used the filter for controlled trial or randomized controlled trial.

### ***Studies selection***

We included studies that were randomized controlled trials of 12 to 52 weeks' duration that included > 10 patients with type 2 diabetes per treatment arm, reported change in HbA1c as the primary endpoint, and studied the effects of adding a single drug (not multiple therapies). Among these, we identified studies that reported data about efficacy of incretins among subgroups of patients, or presented results of a multivariate regression analysis including baseline characteristics of the population.

We excluded duplicates, non-RCTs, unrelated topics and articles not published in English. We excluded studies with a specific population, such as patients with renal impairment, cardiac disease, fasting patients (during Ramadan), pregnant women or women with polycystic ovary syndrome. We excluded papers if the dose or type of administration of the medications were different from those approved by the FDA or European guidelines.

### ***Studies included and data extraction***

We checked that all included papers fulfilled the criteria outlined in Quality Assessment Tool for Quantitative Studies, developed by Effective Public Health Practice Project: [6]. For papers reporting data from the same cohort at different times, we included data from the longest study. One author (HB) extracted the summary of each study, design, number of participants, mean HbA1c and mean change, as data across subgroups when available or conclusion of authors' analysis only. The mean reduction in HbA1c or the percentage of patients reaching an HbA1c < 7.0% were the parameters we examined. We concluded that the treatment showed a differential effect according to different predictor variables if this was

clearly stated in the text, or a statistical analysis describing this effect had been reported. Otherwise we considered a difference greater than 0.2 percentage points between sub-groups to be clinically meaningful.

## **Results**

We identified 4172 papers, and after screening keywords, titles and abstracts, retrieved 209 reports for full text screening (Figure 1). Out of 209 relevant clinical trial reports, 77 included some information on factors that predicted response to incretin therapy; 60 and 17 studies of DPP-4Is and GLP-1As, respectively. Table 1 lists all the factors that were explored in these studies as potential predictors of HbA1c change. The four most common factors examined were baseline HbA1c, age, sex and BMI. However, except for results across HbA1c subgroups, most studies reported only an overall conclusion about predictor response, without providing any details of the analysis.

### ***DPP-4I studies***

Among 60 studies on DPP-4Is, 13 reported data on DPP-4Is as monotherapy, 42 in dual or multiple therapies and five in combination with insulin. There were 47 studies that assessed baseline HbA1c, and 24-38 studies reported on each of the other potential predictors (Table 2). No study reported that lower baseline HbA1c was associated with a greater HbA1c response, although almost 25% of studies reported no association was present. The difference in HbA1c response between patients from the highest baseline HbA1c groups (above 8 or 9%) compared to those in the lowest ones (less than 7%) was less than 0.5 percentage points for most studies; but was 1.1 percentage points in a study of those aged 65 years and above [7], and was 1.8 percentage points in one small study [8]. When we compared studies on DPP-4I that found a relationship between greater efficacy and higher baseline HbA1c (37 studies) with those that did not (10 studies), there was no difference in their baseline characteristics except a greater percentage of men in the studies that reported a relationship (Table 3).

There were 34 studies that found no relationship between HbA1c reduction and age. Three studies reported that patients older than 65 had a greater response compared to those younger, with a small difference between from 0.1 to 0.5 percentage points [9-11], whereas one study

reported the inverse relationship [12]. For gender, 28 studies reported no association, with two reporting a slightly greater response among men [10,13].

For ethnicity, 22 studies found no association between ethnic group and efficacy and 4 found differences across ethnic groups. Greater HbA1c reductions were reported for patients from India and the Philippines than for patients from France or the USA [14] and for Chinese compared to Indian patients [15]. Greater HbA1c reductions were also reported among Asians compared to a predominantly Caucasian group [16].

For BMI, 30 studies reported no relationship between drug efficacy and baseline BMI categories, while six studies described a greater response in patients with BMI < 30 compared to those with a BMI  $\geq$ 30 or 35 [17–22].

Among the studies examining beta cell function, and/or insulin resistance, eight reported no relationship [23–29]. However, one study reported a greater response to alogliptin in patients with reduced beta-cell function (lower baseline levels of fasting C-peptide and HOMA beta) [30], and two studies reported better responses in those with less insulin resistance (lower HOMA-IR) [13,30].

### ***GLP- 1A studies***

We identified 17 studies (13 with exenatide, 4 with liraglutide) reporting on predictors of response to GLP-1A. Table 4 shows that a higher baseline HbA1c was associated with a greater HbA1c reduction in seven studies [31–37], but one study showed the opposite association (higher baseline HbA1c predicted a smaller HbA1c reduction) [38] and a further study reported no association [39]. In studies where there was a significant difference in reduction by different baseline HbA1c, the mean difference between extreme groups was 0.53 percentage points (range 0.23 to 0.8).

Very few studies reported response according to other factors, such as age, gender, race or ethnicity, BMI and known duration of diabetes, and among those that did, the findings were null except for one study that reported an inverse association with BMI and a positive correlation with duration of diabetes [37]. No association between the presence of antibodies status against GLP-1A and HbA1c response was found among 5 studies that examined this.

## Discussion

In this systematic review we included 77 papers that explored the factors that could predict efficacy of incretins. The most robust finding from this review was that higher baseline HbA1c was associated with a greater reduction in HbA1c. However, approximately 25% of studies examining this question found no association, and one study, of a GLP-1A, reported better achievement of a target of HbA1c in those with a lower baseline HbA1c. These findings are in keeping with a recent meta-regression which reported a 0.26% greater reduction in HbA1c with every increase of 1 percentage point of baseline HbA1c [4]. However, Monami et al described an inverse relationship between baseline HbA1c and change in HbA1c in an earlier meta-regression analysis [5]. The meta-regression by Monami was restricted to 33 placebo-controlled trials whereas Esposito included more studies with different previous therapies [4]. Neither of the systematic reviews had access to patient-level data, which may have made them subject to bias (ecological fallacy) [40]. We had no patient-level data. But, in our study, the main characteristics of studies were similar whether they showed an association between baseline HbA1c and efficacy or not. We might speculate that there could be reporting bias, in that analyses showing no relationship might be less likely to be published than those showing a relationship. We should further note that there need to be individual patient-level meta-analysis to fully explore this issue.

Findings in regard to other potential predictors were much weaker, with most studies reporting no associations. Most of our selected studies reported no difference in efficacy according to age. A greater efficacy had been described in older patients in the meta-regression of 44 trials [5] and the inverse relationship was reported by Lim in a multivariate regression analysis of 150 individuals [41]. No effect was observed in the meta-regression by Esposito et al [4].

For BMI, while 30 DPP-4I studies found no association, there were six studies that reported a relationship between BMI and response. In these six studies, lower BMI predicted a better glycaemic response. This was also the conclusion of the meta-regression by Monami [5] et al while BMI was not examined in the meta-regression by Esposito and colleagues [4]. Using individual data, Maeda et al reported in contrary a positive correlation between BMI and reduction in HbA1c with sitagliptin [42] whereas Gautier et al found no association with saxagliptin [43]. Since leaner individuals with type 2 diabetes tend to have a greater insulin secretory defect than do more obese patients, it may be that they respond better to the insulin secretory stimulation that DPP-4Is provide. However, the fact that most studies reported no association, and the possibility that unmeasured confounders may have explained the results in at least some of the six studies reporting the relationship mandates caution over any mechanistic conclusions. Furthermore, we found no evidence of a relationship between estimated beta cell function and response to incretin therapy. Indeed, the relationship with beta cell function has not been assessed in any previous review. We show that among 8 studies, none showed an association between estimated beta cell function and response to drug. However, other authors have reported that lower indices of beta-cell function could be correlated with a greater reduction in HbA1c [41–43].

For ethnicity, only 4/26 studies described a better response in Asian patients. This is in contrast to findings from Monami's study. Although the percentage of Asians included varies between the studies, most of them considered Asian, black and white ethnicities.

For the studies examining efficacy of GLP-1A, this review identified a paucity of data and thus we were not able to draw firm conclusions about which groups of patients could benefit most from this treatment. The majority of studies examining baseline HbA1c reported that higher baseline levels predicted a greater response. Only one study [38] reported the opposite

association but the measure of success was the achievement of a specific HbA1c target, rather than the absolute reduction of HbA1c. It is, therefore, not surprising that lower baseline HbA1c was associated with greater chance of achieving the target. We found no evidence of an effect of exenatide antibodies on HbA1c response.

It is clear that baseline HbA1c is the most readily identifiable predictor of response to incretins, and whilst the majority of studies find that higher baseline HbA1c predicts greater HbA1c lowering, the lack, or even reversal, of this association in a smaller number of studies merits further investigation. However, on its own, HbA1c still fails to explain most of the variability in response. It is noteworthy that for BMI, insulin resistance and ethnicity, even though most studies report no associations, those that do are concordant with each other, showing larger effects in those with lower BMI, less insulin resistance, and in Asian populations. It is not possible to determine whether these are real findings and that methodological issues may have limited the capacity of other trials to identify similar associations, or whether these are chance findings.

An important observation is that most reports of predictors use crude unadjusted analyses. The failure to account for baseline HbA1c in these analyses has at least two important consequences. First, an individual whose HbA1c falls from 7.5 to 6.6% is taken to have responded less well than someone whose HbA1c falls from 9.0 to 8.0%, when it is more likely that the former is the greater responder. Second, the dominance of baseline HbA1c in such simple analyses can obscure important associations of other factors. More sophisticated analyses that account for the influence of baseline HbA1c are required [44].

This review has strengths and limitations. The strength is that we conducted a systematic review and evaluated full text and extracted data about predicting factors of efficacy of

incretin therapies. The main limitation is that we were only able to include the data that the various authors chose to report in each publication. It is likely that there is under-reporting of analyses in which no associations were found, and that in some instances in which null findings were reported, this was due only to lack of statistical power. It was also not possible to standardize the analyses performed, and this may have contributed to the heterogeneity of the results. Another limitation is that we were not able to draw strong conclusions on predictors of incretins efficacy as not many studies reported analyses that considered other factors (ethnicity, BMI, parameters of insulin secretion).

## **Conclusion**

Our review concludes that most studies reported greater response to incretin therapy among patients with higher baseline HbA1c, though this is certainly not a uniform finding. No other factor consistently predicted efficacy of incretin therapy. Thus, in the face of a growing number of glucose-lowering drug classes, the available data from the literature do not allow us to draw the profile of the best candidate for one of these classes. We advocate for pooling of individual data from multiple studies, and for the use of statistical approaches that account for the effect of baseline HbA1c, in order to provide information for clinicians and patients to guide the selection of therapy. Increasing costs of therapy, the potential for adverse-effects of therapy, and the increasing number of drug choices mean that tools to assist with drug selection are urgently needed.

**Declaration of interests**

The authors declare that there are no conflicts of interest.

**Authors' contribution**

HB researched the data and wrote the manuscript. JS directed the research and reviewed/edited the manuscript. WLN researched the data and contributed to the discussion. DJM reviewed/edited the manuscript. All authors contributed to the interpretation of the results and the revision of the manuscript for intellectual content and approved the final version of the manuscript.

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Figure

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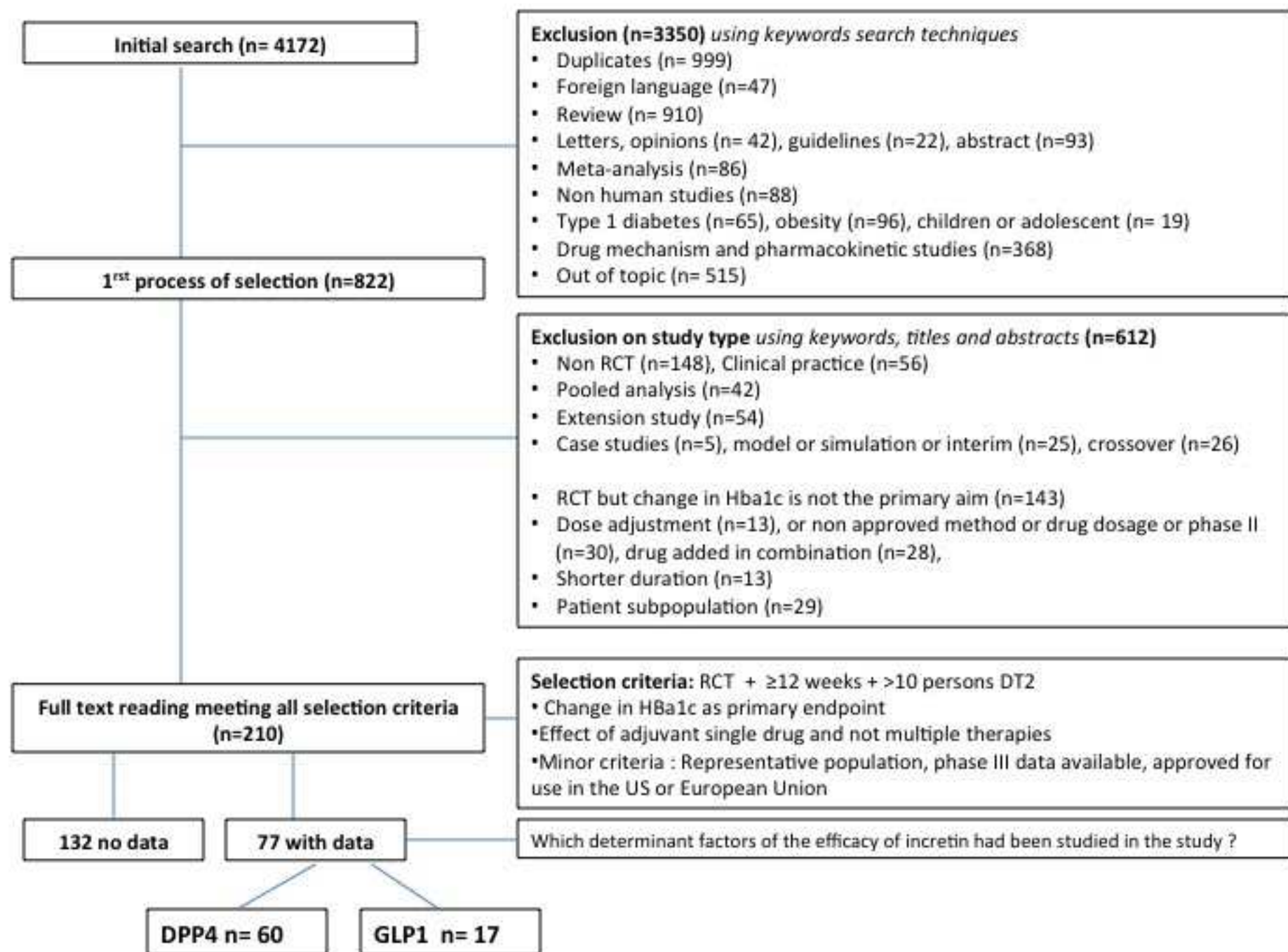


**Table 1:** List of determinant factors

| Factors                      | Thresholds used                                        |
|------------------------------|--------------------------------------------------------|
| Baseline HbA1c               | All values                                             |
| Gender                       | Men, Women                                             |
| Age                          | Median, 65 years                                       |
| Race and ethnicity           | White, Black, Hispanic, Asian, others                  |
| BMI                          | Median, 30 kg/m <sup>2</sup>                           |
| Metabolic syndrome           | Presence or absence                                    |
| Known duration of diabetes   | Median, 1 or 5 years                                   |
| HOMA-B                       | Median                                                 |
| HOMA-IR                      | Median                                                 |
| Pro-insulin to insulin ratio | Median                                                 |
| C-peptide level              | Median                                                 |
| Background therapies         | Sub-group according to the class of background therapy |
| GLP-1A antibodies            | Median, low or high titer                              |
| eGFR                         | < 60 and < 90 ml/min                                   |
| Hepatobiliary disease        | Presence or absence                                    |

**Table 2:** Relationship of baseline factors to HbA1c lowering in DPP-4I trials.

|                               | Type of association reported (number of studies) |                |          |
|-------------------------------|--------------------------------------------------|----------------|----------|
|                               | None*                                            | Positive       | Negative |
| Monotherapy                   |                                                  |                |          |
| Baseline HbA1c                | 0                                                | 11             | 0        |
| Age                           | 6                                                | 0              | 0        |
| Gender                        | 7                                                | 0              | 0        |
| Race or ethnicity             | 7                                                | 0              | 0        |
| BMI                           | 7                                                | 0              | 2        |
| Known duration of diabetes    | 3                                                | 1              | 1        |
| Dual or multiple oral therapy |                                                  |                |          |
| Baseline HbA1c                | 9                                                | 24             | 0        |
| Age                           | 26                                               | 2              | 1        |
| Gender                        | 19                                               | 2 <sup>a</sup> | 0        |
| Race or ethnicity             | 14                                               | 2 <sup>b</sup> | 0        |
| BMI                           | 20                                               | 0              | 4        |
| Known duration of diabetes    | 17                                               | 0              | 1        |
| Add-on to insulin             |                                                  |                |          |
| Baseline HbA1c                | 1                                                | 2              | 0        |
| Age                           | 2                                                | 1              | 0        |
| Gender                        | 2                                                | 0              | 0        |
| Race or ethnicity             | 1                                                | 2 <sup>b</sup> | 0        |
| BMI                           | 3                                                | 0              | 0        |
| Known duration of diabetes    | 1                                                | 1              | 0        |
| All studies                   |                                                  |                |          |
| Baseline HbA1c                | 10                                               | 37             | 0        |
| Age                           | 34                                               | 3              | 1        |
| Gender                        | 28                                               | 2 <sup>a</sup> | 0        |
| Race or ethnicity             | 22                                               | 4 <sup>b</sup> | 0        |
| BMI                           | 30                                               | 0              | 6        |
| Known duration of diabetes    | 21                                               | 2              | 2        |

\* The association was examined, but was reported to be absent, <sup>a</sup> greater response in men in both studies, <sup>b</sup> in those studies, a greater decrease in HbA1c has been reported in some ethnic group.

**Table 3:** Comparison of DPP-4I RCTs reporting baseline HbA1c to be a predictor of change in HbA1c, with RCTs finding no association.

|                                 | Studies that showed a link | Studies with no link | T-Test or Chi2 |
|---------------------------------|----------------------------|----------------------|----------------|
| n                               | 37                         | 10                   |                |
| Length (weeks)                  | 29.8 ± 13.5                | 24.4 ± 10.9          | 0.25           |
| Drugs                           |                            |                      |                |
| • Monotherapy                   | 11                         | 0                    |                |
| • Bi or multiple therapy        | 25                         | 9                    |                |
| • Add on insulin                | 2                          | 1                    | 0.17           |
| Number of subjects              | 249.8 ± 191.4              | 212.3 ± 123.0        | 0.56           |
| Baseline HbA1c (%)              | 8.1 ± 0.5                  | 8.3 ± 0.4            | 0.37           |
| Age, (years)                    | 57.7 ± 4.2                 | 55.3 ± 1.7           | <b>0.04</b>    |
| BMI, (kg/m <sup>2</sup> )       | 29.2 ± 2.9                 | 29.6 ± 3.5           | 0.73           |
| Men (%)                         | 56.7 ± 9.1                 | 53.2 ± 5.3           | 0.25           |
| Duration of diabetes (years)    | 7.7 ± 9.9                  | 6.8 ± 2.4            | 0.76           |
| Fasting plasma glucose (mmol/L) | 9.6 ± 0.8                  | 9.4 ± 0.4            | 0.27           |

Values are reported as means and SD. For drugs, the number of studies is reported by each combination of treatments.

**Table 4:** Relationship of baseline factors to HbA1c lowering in GLP-1A trials

| Factor                     | Type of association reported (number of studies) |          |          |
|----------------------------|--------------------------------------------------|----------|----------|
|                            | None*                                            | Positive | Negative |
| Baseline HbA1c             | 1                                                | 7        | 1        |
| Age                        | 3                                                | 0        | 0        |
| Gender                     | 3                                                | 0        | 0        |
| Race or ethnicity          | 1                                                | 0        | 0        |
| BMI                        | 3                                                | 0        | 1        |
| Known duration of diabetes | 0                                                | 1        | 0        |

\* The association was examined, but was reported to be absent.

Supplementary Table 2: Factors evaluated in DPP-4I studies

| DPP-4I in Monotherapy |                  |                | Summary of the Study |                         |           |                         |                    | Reported Predictive Factors of the Response |                |                 |     |        |        |        |                 |                        |
|-----------------------|------------------|----------------|----------------------|-------------------------|-----------|-------------------------|--------------------|---------------------------------------------|----------------|-----------------|-----|--------|--------|--------|-----------------|------------------------|
|                       | Author, Year     | Length (weeks) | Add-on to            | Drugs                   | N         | Baseline HbA1c          | Change             | Difference between groups                   | Baseline HbA1c | AGE             | SEX | Ethn.* | BMI    | Durat. | Other           |                        |
| 1                     | Aschner, 2006    | 24             | None                 | Sitagliptin 100mg       | 238       | 8.01±0.88               | 0.18±0.06, (0.30)  | Dgp -0.61±0.74, (-0.49)                     | yes(+)         | no              | no  | no     | no     |        |                 |                        |
| Sitagliptin 200mg     |                  |                |                      | 250                     | 8.08±0.94 | Dgp -0.76±0.88, (-0.64) |                    |                                             |                |                 |     |        |        |        |                 |                        |
| Placebo               |                  |                |                      | 253                     | 8.03±0.82 |                         |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 2                     | Aschner, 2010    | 24             | None                 | Sitagliptin 100mg       | 455       | 7.2±0.7                 | -0.45±0.48, (0.38) | Dgp -0.14±0.06, (0.21)                      | yes(+)         | no              | no  | no     | no     | no     |                 |                        |
| Metformine            |                  |                |                      | 439                     | 7.2±0.7   | -0.57±0.62, (0.51)      |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 3                     | Barzilai, 2011   | 24             | None                 | Sitagliptin 50 or 100mg | 101       | 7.8±0.8                 | -0.5±0.7, (0.2)    | Dgp -0.7±0.9, (0.5)                         | yes(+)         | no <sup>a</sup> | no  | no     | no     | yes(+) |                 |                        |
| Placebo               |                  |                |                      | 91                      | 7.7±0.7   | 0.2±0.0, (0.5)          |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 4                     | Del Prato, 2011  | 24             | None                 | Linagliptin 5mg         | 336       | 8±0.05                  | 0.25±0.07          | Dgp -0.69±0.08 (-0.85, 0.53)                | yes(+)         |                 | no  | no     | no     | no     | no <sup>b</sup> |                        |
| Placebo               |                  |                |                      | 167                     | 8.0±0.07  |                         |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 5                     | Iwamoto, 2010    | 12             | None                 | Vildagliptin 100mg      | 188       | 7.5±0.9                 |                    | Dgp -0.57±0.06 (-0.68, 0.46)                | yes(+)         | no              | no  |        | no     |        |                 |                        |
| Voglibose 0.2mg       |                  |                |                      | 192                     | 7.6±0.9   |                         |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 6                     | Mohan, 2009      | 18             | None                 | Sitagliptin 100mg       | 352       | 8.7±1.0                 | -0.7±0.8, (0.6)    | Dgp -1.0±1.2, (0.8)                         |                | no              | no  | no     | no     | no     | no <sup>c</sup> |                        |
| Placebo               |                  |                |                      | 178                     | 8.8±1.1   |                         |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 7                     | Pan, 2008        | 24             | None                 | Vildagliptin 100mg      | 441       | 8.6±0.9                 | -1.4±0.1           | Dgp -0.1±0.1, (-0.308)                      | yes(+)         |                 |     |        | yes(-) |        |                 |                        |
| Acarbose 300mg        |                  |                |                      | 220                     | 8.6±1.0   | -1.3±0.1                |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 8                     | Pan, 2012        | 24             | None                 | Saxagliptin 5mg         | 284       | 8.1±0.8                 | -0.84              |                                             |                |                 |     | no     |        |        |                 |                        |
| Placebo               |                  |                |                      | 284                     | 8.2±0.8   | -0.34                   |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 9                     | Raz, 2006        | 18             | None                 | Sitagliptin 100mg       | 193       | 8.04±0.89               | -0.48±0.61, (0.35) | Dgp -0.60±0.82, (0.39)                      | yes(+)         | no              | no  | no     | no     | yes(-) | no <sup>d</sup> |                        |
| Sitagliptin 200mg     |                  |                |                      | 199                     | 8.14±0.91 | -0.36±0.48, (0.23)      |                    |                                             |                |                 |     |        |        |        |                 | Dgp -0.48±0.70, (0.26) |
| Placebo               |                  |                |                      | 103                     | 8.05±0.90 | 0.12±0.05, (0.3)        |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 10                    | Rosenstock, 2007 | 24             | None                 | Vildagliptin 100mg      | 519       | 8.7±1.1                 | -1.1±0.1           |                                             | yes(+)         |                 |     |        | yes(-) |        |                 |                        |
|                       |                  |                |                      | Rosiglitazone 8mg       | 267       | 8.7±1.1                 | -1.3±0.1           |                                             |                |                 |     |        |        |        |                 |                        |
| 11                    | Rosenstock, 2009 | 24             | None                 | Saxagliptin 2.5mg       | 102       | 7.9±0.9                 | 7.5                |                                             | yes(+)         |                 |     |        |        |        |                 |                        |
| Saxagliptin 5mg       |                  |                |                      | 106                     | 8.0±1.1   | 7.5                     |                    |                                             |                |                 |     |        |        |        |                 |                        |
| Saxagliptin 10mg      |                  |                |                      | 98                      | 7.8±0.9   | 7.3                     |                    |                                             |                |                 |     |        |        |        |                 |                        |
| Placebo               |                  |                |                      | 95                      | 7.9±0.9   | 8.1                     |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 12                    | Schweizer, 2007  | 52             | None                 | Vildagliptin 100mg      | 526       | 8.7±1.1                 | -1.0±0.1           |                                             | yes(+)         |                 |     |        |        |        |                 |                        |
| Metformine 2000mg     |                  |                |                      | 254                     | 8.7±1.1   | -1.4±0.1                |                    |                                             |                |                 |     |        |        |        |                 |                        |
| 13                    | Schweizer, 2009  | 24             | None                 | Vildagliptin 100mg      | 169       | 7.8±0.6                 | -0.64±0.07         |                                             | yes(+)         |                 |     |        |        |        |                 |                        |
| Metformine 1500mg     |                  |                |                      | 166                     | 7.7±0.6   | -0.75±0.07              |                    |                                             |                |                 |     |        |        |        |                 |                        |

\* For ethnicity, “Yes” means that a greater decrease in HbA1c has been reported in some ethnic group in those studies. <sup>a</sup> The included population of this study was restricted to people older than 65 years. <sup>b</sup> Del Prato et al found no link between efficacy and geographical region, number of previous antidiabetic drugs, presence of metabolic syndrome at baseline, baseline HOMA-IR, HOMA-B, and proinsulin/insulin ratio. <sup>c</sup> There were no difference among subgroups according to HOMA beta, HOMA IR or insulinogenic index <sup>d</sup> There were no difference among subgroups according to HOMA-IR, HOMA-B and baseline metabolic status

| DPP-4 Inhibitor Therapy |         |                                      | Summary of the Study                                                                   |                            |                                                     |                                                          |                                                 | Reported Predictive Factors of the Response |                 |     |        |        |        |                 |  |
|-------------------------|---------|--------------------------------------|----------------------------------------------------------------------------------------|----------------------------|-----------------------------------------------------|----------------------------------------------------------|-------------------------------------------------|---------------------------------------------|-----------------|-----|--------|--------|--------|-----------------|--|
| Author, Year            | (weeks) | Add-on to                            | Drugs                                                                                  | N                          | Baseline HbA1c                                      | Change                                                   | Diff. between groups                            | Baseline                                    | AGE             | SEX | Ethn.* | BMI    | Durat. | Other           |  |
| 1 Bajaj, 2014           | 24      | Metformin + Pioglitazone             | Linagliptin 5mg<br>Placebo                                                             | 183<br>89                  | 8.39±0.84<br>8.47±0.78                              | -0.84±0.11<br>-0.27±(0.13)                               | Dgp±0.57±(0.13)                                 |                                             |                 |     | yes    |        |        |                 |  |
| 2 Barnett, 2013         | 24      | Metformin or SU or basal insulin     | Linagliptin 5mg<br>Placebo                                                             | 160<br>78                  | 7.8±0.8<br>for all                                  | -0.61±(0.06)<br>-0.56±(0.24)                             | Dgp±1.15±(-1.68, 0.62)                          |                                             | no <sup>a</sup> |     |        |        | no     | no <sup>b</sup> |  |
| 3 Bolli, 2009           | 52      | Metformin                            | Vildagliptin 50mg bid<br>Pioglitazone 30mg                                             | 295<br>281                 | 8.4±1.0<br>8.4±0.9                                  | -0.6±(-0.71, 0.45)<br>-0.6±(-0.77, 0.52)                 |                                                 | yes(+)                                      | no              |     |        | yes(-) |        |                 |  |
| 4 Bosi, 2007            | 24      | Metformin                            | Vildagliptin 50mg<br>Vildagliptin 100mg<br>Placebo                                     | 177<br>185<br>182          | 8.4±0.1<br>8.4±0.1<br>8.3±0.9                       | -0.7±0.1<br>-1.1±0.1<br>0.2±0.1                          |                                                 | no                                          |                 |     |        |        |        |                 |  |
| 5 Bosi, 2011            | 52      | Metformin + Pioglitazone 30          | Alogliptin 25mg<br>Pioglitazone 15mg                                                   | 303<br>306                 | 8.3±0.82<br>8.1±0.83                                | -0.31±(0.068)<br>-0.05±(0.061)                           | Dgp±0.26±(-0.45, 0.08)                          | no                                          | no              |     | no     | no     |        |                 |  |
| 6 Chacra, 2009          | 24      | Glyburide 7.5mg                      | Saxagliptin 2.5mg<br>Saxagliptin 5mg<br>15mg qmx                                       | 248<br>253<br>267          | 8.4±0.9<br>8.5±0.9<br>8.4±0.9                       | -0.54<br>-0.64<br>0.08                                   |                                                 | no                                          | no              | no  | no     | no     | no     |                 |  |
| 7 Charbonnel, 2006      | 24      | Metformin                            | Sitagliptin 100mg<br>Placebo                                                           | 464<br>237                 | 7.96±0.81<br>8.03±0.82                              | Dgp±0.67±(-0.77, -0.57)<br>±0.02±(-0.15, -0.10)          |                                                 | no                                          |                 |     |        |        |        | no <sup>c</sup> |  |
| 8 DeFronzo, 2009        | 24      | Metformin                            | Saxagliptin 2.5mg<br>Saxagliptin 5mg<br>Saxagliptin 10mg<br>Placebo                    | 192<br>191<br>181<br>179   | 8%<br>for all<br>-0.58±0.07<br>0.13±0.07            | -0.59±0.07<br>-0.69±0.07<br>-0.58±0.07<br>0.13±0.07      | Dgp±0.73±0.10<br>Dgp±0.83±0.10<br>Dgp±0.72±0.10 | yes(+)                                      | no              | no  | no     | no     | no     |                 |  |
| 9 Dobs, 2013            | 18      | Metformin 2550mg + Pioglitazone 24mg | Sitagliptin 100mg<br>Placebo                                                           | 170<br>92                  | 8.8±1.0<br>8.7±1.0                                  | -0.3±(-0.5, 0.1)<br>-1.0±(-1.2, 0.9)                     | Dgp±0.7±(1.0, 0.5)                              | yes(+)                                      | no              | no  | no     | no     | no     | no <sup>d</sup> |  |
| 10 Filozof, 2010        | 24      | Metformin 1000mg                     | Vildagliptin 100mg<br>Metformine 1500-1000                                             | 456<br>458                 | 7.4±0.78<br>7.3±0.79                                | -0.51<br>-0.37                                           | Dgp±0.14±(0.24, 0.05)                           | yes(+)                                      | no              |     |        | no     |        |                 |  |
| 11 Filozof, 2010        | 24-52   | Metformin 1500mg                     | Vildagliptin 100mg<br>Glicazide up to 320mg                                            | 513<br>494                 | 8.5±1.0<br>8.5±1.0                                  | 1.01±0.24<br>-0.85±(0.06)                                |                                                 | yes(+)                                      | no              | no  |        | no     |        |                 |  |
| 12 Fonseca, 2013        | 26      | Metformin 2550mg + Pioglitazone 30mg | Sitagliptin 100mg<br>Placebo                                                           | 157<br>150                 | 8.8±1.0<br>8.7±1.0                                  | -1.1±(-1.3, 0.1)<br>-0.4±(-0.5, 0.3)                     | Dgp±0.7±(-0.9, 0.5)                             | yes(+)                                      |                 |     |        |        |        |                 |  |
| 13 Forst, 2010          | 12      | Metformin                            | Linagliptin 1mg<br>Linagliptin 5mg<br>Linagliptin 10mg<br>Placebo<br>Glimepiride 1-3mg | 65<br>66<br>66<br>71<br>66 | 8.2±0.7<br>8.5±0.8<br>8.4±0.7<br>8.4±0.7<br>8.2±0.7 | -0.14±0.92<br>-0.5±0.81<br>-0.42±0.87<br>0.24±0.74<br>NA |                                                 | yes(+)                                      | no              | no  | no     | no     | no     |                 |  |
| 14 Garber, 2008         | 24      | Glimepiride 4mg                      | Vildagliptin 50<br>Vildagliptin 100<br>Placebo                                         | 132<br>132<br>144          | 8.5±0.9<br>8.6±1.0<br>8.5±1.0                       | -0.58±0.10<br>±0.13<br>0.07±0.09                         | Dgp±0.63±0.9                                    | yes(+)                                      | yes(+)          |     |        |        |        |                 |  |
| 15 Goke, 2010           | 52      | Metformin                            | Saxagliptin 5<br>glipizide 5-20mg                                                      | 428<br>430                 | 7.46±(0.045)<br>7.53±(0.045)                        | -0.74<br>-0.80                                           | Dgp±0.06±(0.053)<br>(-0.05, 0.16)               | yes(+)                                      |                 |     |        |        |        |                 |  |

| DPP-4 Inhibitor Therapy |                   |    | Summary of the Study    |                                                                                                                  |                             | Reported Predictive Factors of the Response            |                                                             |                                                                                             |        |    |                  |    |    |                 |                 |  |
|-------------------------|-------------------|----|-------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------|----|------------------|----|----|-----------------|-----------------|--|
| 16                      | Hermansen, 2007   | 24 | Glimepiride ± Metformin | Sitagliptin 100mg<br>Placebo                                                                                     | 222<br>219                  | 8.34±0.76<br>8.34±0.74                                 | -0.45(-0.57,0.34)                                           | Dgp0.74(-0.9,-0.57)                                                                         | yes(+) | no | no               | no | no | no              |                 |  |
| 17                      | Inagaki, 2013     | 52 | Monotherapies           | Linagliptin(+metformin)<br>Linagliptin(+glinide)<br>Linagliptin(+glitazone)<br>Linagliptin+SU<br>Linagliptin+AGI | 82<br>63<br>73<br>140<br>85 | 8.0±0.8<br>7.9±0.82<br>7.9±0.82<br>8.1±0.8<br>7.9±0.82 | -0.9±0.6<br>-0.7±0.7<br>-0.8±0.5<br>-0.7±0.72<br>-0.9±0.62  |                                                                                             | yes(+) | no |                  |    | no | no <sup>e</sup> |                 |  |
| 18                      | Jeon, 2011        | 32 | Metformin 1000mg        | Vildagliptin 100mg<br>Glimepiride 2mg                                                                            | 51<br>51                    | 8.01±1.2<br>8.13±0.862                                 | -1.15±0.94<br>-1.32±1.00                                    |                                                                                             | yes(+) |    |                  |    |    |                 |                 |  |
| 19                      | Kaku, 2011        | 12 | Pio.15-30mg             | Alogliptin 12.5mg<br>Alogliptin 25mg<br>Placebo                                                                  | 111<br>113<br>115           | 7.91±0.82<br>7.89±0.73<br>7.92±0.85                    | -0.90±0.44<br>-0.97±0.52<br>-0.19±0.55                      |                                                                                             | yes(+) | no | no               |    | no | no              | yes             |  |
| 20                      | Kawamori, 2012    | 26 | None, monotherapy       | Linagliptin 5mg<br>Linagliptin 10mg<br>Placebo<br>Voglibose                                                      | 159<br>160<br>80<br>162     | 8.07(0.05)<br>7.98(0.05)<br>7.95(0.07)<br>8.02(0.06)   | -0.13(0.07)<br>-0.19(0.07)<br>0.19(0.07)<br>-0.26(0.07)     | Dgp0.32(-0.49,-0.15)<br>Dgp0.39(-0.56,-0.21)                                                | yes(+) |    |                  |    |    | no              |                 |  |
| 21                      | Kikuchi, 2010     | 12 | Glimepiride 2-1mg       | Vildagliptin 100mg<br>Placebo                                                                                    | 102<br>100                  | 7.8±0.8<br>8.0±0.8                                     | -1.0(0.063e)<br>-0.060.06                                   | Dgp0.95(0.08)                                                                               | yes(+) | no | no               |    | no |                 | no <sup>f</sup> |  |
| 22                      | Lewin, 2012       | 18 | SU+otherOAD             | Linagliptin 5mg<br>Placebo                                                                                       | 161<br>84                   | 8.6±0.9<br>8.6±0.72                                    | -0.54(0.07se)                                               | Dgp-0.47(-0.7,0.24)                                                                         |        |    |                  |    |    |                 | no <sup>e</sup> |  |
| 23                      | Li, 2014          | 24 | Metformin               | Vildagliptin 100mg<br>Saxagliptin 5mg<br>Sitagliptin 100mg                                                       | 63<br>66<br>61              | 8.75±1.15<br>8.86±1.13<br>8.54±1.19                    | -1.34(-2.03,0.64)<br>-1.21(-1.91,0.51)<br>-1.07(-1.64,0.50) | vsVilda./Vilda./saxa.:<br>Dgp0.13(-0.66,0.40)<br>Dgp0.27(-0.80,0.26)<br>Dgp0.14(-0.67,0.39) |        | no |                  |    |    | no              |                 |  |
| 24                      | Liu, 2013         | 24 | Metformin +SU 1/2dose   | Sitagliptin 100mg<br>Pioglitazone 30mg                                                                           | 60<br>59                    | 8.54±0.97<br>8.27±0.862                                | -0.71±0.12<br>-0.94±0.12                                    | Dgp0.23±0.17                                                                                | yes(+) | no | yes <sup>e</sup> |    | no | no              | no              |  |
| 25                      | Lukashevich, 2014 | 24 | Metformin ±otherOAD     | Vildagliptin 100mg<br>Placebo                                                                                    | 158<br>160                  | 8.7±0.9<br>8.8±0.92                                    | -1.01<br>-0.25                                              | Dgp0.77                                                                                     | no     | no | no               | no | no |                 |                 |  |
| 26                      | Nauck, 2009       | 26 | Metformin               | Alogliptin 12.5mg<br>Alogliptin 25mg<br>Placebo                                                                  | 213<br>210<br>104           | 7.9±0.7<br>7.9±0.8<br>8.0±0.92                         | -0.6(0.1)<br>-0.6(0.1)<br>-0.10.1                           |                                                                                             |        | no | no               | no | no |                 |                 |  |
| 27                      | Nauck, 2007       | 52 | Metformin 2x1500mg      | Sitagliptin 100mg<br>Glipizide 5mg                                                                               | 588<br>584                  | 6.84±0.66<br>6.86±0.69                                 | -0.67(-0.75,0.59)                                           | Dgp0.01(-0.09,0.08)                                                                         | yes(+) |    |                  |    |    |                 |                 |  |
| 28                      | Nonaka, 2008      | 12 | None, metformin orSU    | Sitagliptin 100mg<br>Placebo                                                                                     | 75<br>76                    | 7.54±0.85<br>7.69±0.862                                | -0.65(-0.8,0.5)                                             | Agp1.05(-1.27,0.84)                                                                         | no     | no | no               |    | no | no              |                 |  |
| 29                      | Owens, 2011       | 24 | Metformin+SU            | Linagliptin 5mg<br>Placebo                                                                                       | 792<br>263                  | 8.15(0.03)<br>8.14(0.05)                               | -0.72(0.03)<br>-0.10(0.05),                                 | Dgp0.62(0.06)<br>(-0.73,0.50)                                                               | yes(+) |    | no               |    |    |                 |                 |  |

| DPP-4 Inhibitor therapy |                  |    |                      | Summary of the Study |     |            |                     | Reported predictive factors of the response |        |        |        |        |        |        |                 |
|-------------------------|------------------|----|----------------------|----------------------|-----|------------|---------------------|---------------------------------------------|--------|--------|--------|--------|--------|--------|-----------------|
| 30                      | Odawara, 2014    | 12 | Metformin            | Vildagliptin 100mg   | 69  | 8.0±0.83   | -1.1±0.06           | Dgp±1.0±0.10                                |        | no     | no     |        | yes(-) |        |                 |
|                         |                  |    |                      | Placebo              | 70  | 8.0±0.96   | -0.1±0.06           |                                             |        |        |        |        |        |        |                 |
| 31                      | Pan, 2012        | 24 | Metformin            | Vildagliptin 100mg   | 146 | 8.09±0.85  | -1.05±(0.05)        | Dgp±0.51±0.12                               | no     | yes(-) |        |        | yes(-) | yes(-) | yes             |
|                         |                  |    |                      | Vildagliptin 50mg    | 148 | 8.05±0.84  | -0.92±(0.08)        |                                             |        |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 144 | 8.01±0.82  | -0.54±(0.08)        |                                             |        |        |        |        |        |        |                 |
| 32                      | Pratley, 2009    | 26 | Pioglitazone         | Alogliptin 12.5mg    | 197 | 8.1±0.9    | -0.66               |                                             | yes(+) | no     |        | no     | no     |        |                 |
|                         |                  |    |                      | Alogliptin 25mg      | 199 | 8.0±0.8    | -0.80               |                                             |        |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 97  | NA         | -0.19               |                                             |        |        |        |        |        |        |                 |
| 33                      | Pratley, 2009    | 26 | SU                   | Alogliptin 12.5mg    | 203 | 55.8±8%    | -0.39               |                                             | yes(+) | yes(+) | yes(+) | yes(+) | yes(-) |        |                 |
|                         |                  |    |                      | Alogliptin 25mg      | 198 | for all    | -0.53               |                                             |        |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 99  |            | +0.01               |                                             |        |        |        |        |        |        |                 |
| 34                      | Raz, 2008        | 30 | Metformin            | Sitagliptin 100mg    | 96  | 9.3±0.9    | -1.0±(-1.3, 0.7)    | Dgp±1.0±(-1.4, 0.6)                         | yes(+) | no     | no     | no     | no     | no     | no <sup>h</sup> |
|                         |                  |    |                      | Placebo              | 96  | 9.1±0.83   | 0.0±(-0.2, 0.3)     |                                             |        |        |        |        |        |        |                 |
| 35                      | Rosenstock, 2006 | 24 | Pioglitazone 30-45mg | Sitagliptin 100mg    | 163 | 8.05±0.81  | -0.85±(-0.98, 0.72) | Dgp±0.70±(-0.85, 0.54)                      | yes(+) | no     | no     | no     | no     | no     |                 |
|                         |                  |    |                      | Placebo              | 174 | 8.00±0.83  | -0.15±(-0.28, 0.03) |                                             |        |        |        |        |        |        |                 |
| 36                      | Seino, 2011      | 12 | Voglibose 0.6mg      | Alogliptin 12.5mg    | 76  | 8.02±0.99  | -0.96±(0.55)        |                                             |        | no     | no     |        |        | no     |                 |
|                         |                  |    |                      | Alogliptin 25mg      | 79  | 7.91±0.91  | -0.91±(0.48)        |                                             |        |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 75  | 8.12±1.19  | +0.04±(0.46)        |                                             |        |        |        |        |        |        |                 |
| 37                      | Scott, 2008      | 18 | Metformin            | Sitagliptin 100mg    | 94  | 7.8±1.0    | -0.73±(-0.87, 0.6)  | Dgp±0.51±(-0.7, 0.32)                       | yes(+) | no     | no     | no     | no     | no     |                 |
|                         |                  |    |                      | Rosiglitazone 8mg    | 87  | 7.73±0.81  | -0.75±0.92±0.65     |                                             |        |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 92  | 7.68±0.88  | -0.22±0.36±0.08     |                                             |        |        |        |        |        |        |                 |
| 38                      | Taskinen, 2011   | 24 | Metformin            | Linagliptin 5mg      | 523 | 8.09±0.04  | 0.5)                | Dgp±0.64±0.08                               | yes(+) |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 177 | 8.02±0.07  | 0.15±0.06           |                                             |        |        |        |        |        |        |                 |
| 39                      | White, 2014      | 12 | Metformin            | Saxagliptin 5mg      | 74  | 7.92±0.961 | -0.56±(0.09)        | Dgp±0.34±(0.12)                             | no     | no     | no     | no     |        |        |                 |
|                         |                  |    |                      | Placebo              | 86  | 7.97±0.819 | -0.22±(0.08)        |                                             |        |        |        |        |        |        |                 |
| 40                      | Yang, 2012       | 24 | Metformin            | Sitagliptin 100mg    | 197 | 8.5±0.9    | -1±(-1.2, 0.9)      | Dgp±0.9±(-1.1, 0.7)                         |        | no     | no     |        | no     | no     | no <sup>i</sup> |
|                         |                  |    |                      | Placebo              | 198 | 8.5±0.9    | -0.1±(-0.3, 0)      |                                             |        |        |        |        |        |        |                 |
| 41                      | Yang, 2011       | 24 | Metformin            | Saxagliptin 5mg      | 283 | 7.9±0.8    | -0.78               | Dgp±0.42±(-0.55, 0.29)                      |        |        |        | no     |        |        |                 |
|                         |                  |    |                      | Placebo              | 287 | 7.9±0.9    | -0.37               |                                             |        |        |        |        |        |        |                 |
| 42                      | Yang, 2014       | 24 | MonoT2               | Vildagliptin 50mg    | 143 | 8.6±0.9    | -0.7±0.1            | Dgp±0.5±0.2                                 | no     |        |        |        |        |        |                 |
|                         |                  |    |                      | Placebo              | 136 | 8.7±1.0    | -0.2±0.1            |                                             |        |        |        |        |        |        |                 |

<sup>a</sup> The included population of this study was restricted to people older than 70 years. <sup>b</sup> There was no difference according to renal function categories, nor previous therapies. <sup>c</sup> There was no difference according to previous therapies. <sup>d</sup> There was no difference according to HOMA-IR and HOMA beta (threshold =median) <sup>e</sup> Inagaki et al reported many details, among those subgroups of eGFR (60ml/min, 90 ml/min) or presence of hepatobilar disorder, without showing differences in efficacy. <sup>f</sup> There was no difference according to previous dose of glimepiride, nor eGFR. <sup>g</sup> There was no difference according to background treatment with one or two drugs. <sup>h</sup> There was no difference according to background treatment (metformin alone or in combination), and HOMA-IR, HOMA-B <sup>i</sup> There was no difference according to background dose of metformin.

| DPP-4 and Insulin Therapy |                |                        | Summary of the Study                            |                   |                               | Reported Predictive Factors of the Response |                        |                |        |     |                  |     |        |                 |
|---------------------------|----------------|------------------------|-------------------------------------------------|-------------------|-------------------------------|---------------------------------------------|------------------------|----------------|--------|-----|------------------|-----|--------|-----------------|
| Author, Year              | Length (weeks) | Add-on to              | Drugs                                           | N                 | Baseline HbA1c                | Change                                      | D between groups       | Baseline HbA1c | AGE    | SEX | Ethn.*           | BMI | Durat. | Other           |
| 1 Fonseca, 2007           | 24             | Insulin                | Vildagliptin 100mg<br>Placebo                   | 144<br>152        | 8.4±1.0<br>8.4±1.1            | -0.5±0.1<br>-0.2±0.1                        | Dgp 0.3±0.1            |                | yes(+) |     |                  | no  |        |                 |
| 2 Kozlovski, 2013         | 24             | Insulin<br>±met.1500mg | Vildagliptin 100mg<br>Placebo                   | 85<br>84          | 8.9±1.0<br>9.0±1.0            | -0.8±0.2<br>-0.03±0.2                       | Dgp 0.82±0.2           |                |        |     | yes <sup>a</sup> |     |        |                 |
| 3 Rosenstock, 2009        | 26             | Insulin + DAD          | Alogliptin 12.5mg<br>Alogliptin 25mg<br>Placebo | 131<br>129<br>130 | 9.3±1.1<br>9.3±1.1<br>9.3±1.1 | -0.63<br>-0.71<br>-0.13                     |                        | yes(+)         |        |     |                  |     |        |                 |
| 4 Visboll, 2010           | 24             | Insulin                | Sitagliptin 100mg<br>Placebo                    | 322<br>319        | 8.7±0.9<br>8.6±0.9            | -0.6<br>0                                   |                        | no             | no     | no  | no               | no  | no     |                 |
| 5 Yki-Jarvinen, 2013      | 52             | Insulin                | Linagliptin 5mg<br>Placebo                      | 631<br>630        | 8.31±0.85<br>8.29±0.85        | -0.48±0.08<br>0.05±0.08 (52w)               | Dgp 0.53 (-0.64, 0.43) | yes(+)         | no     | no  | yes              | no  | yes(+) | no <sup>a</sup> |

<sup>a</sup> There was no difference according to background therapy (insulin or oral anti diabetic treatment, nor renal function)

**Supplementary Table 4:** Factors evaluated in GLP-1A studies

<sup>a</sup> Buse is an extension study of Drucker study, met. metformin,  $\Delta$ gp difference between the treatment group and the control group (placebo or active comparator)





## Supplemental Appendix

## References of all included DPP4 studies

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