Differential HbA1c response in the placebo arm of DPP-4 inhibitor clinical trials conducted in China compared to other countries: a systematic review and meta-analysis

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Abstract

Background: It has been observed that the efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors as compared to the placebo groups in some clinical trials conducted in China is weaker than that in trials conducted outside China, leading to the suspicion that this may be caused by differential Glycosylated Hemoglobin (HbA1c) response in the placebo arm of DPP-4 inhibitor clinical trials conducted in China compared to other countries.

Methods: We searched published articles and other documents related to phase III placebo-control trials of DPP-4 inhibitors in Type 2 diabetes mellitus (T2DM). We included studies from different countries and compared those conducted in China to those conducted in other countries. Meta-regression analysis was used to analyze the HbA1c response in the placebo arms.

Results: A total of 66 studies met the inclusion criteria and 10 were conducted within China. There were a total of 8303 participants (mean age 56, male 57 %) in placebo groups. The pooled change in HbA1c for the placebo groups of 10 trials conducted in patients with T2DM in China was 0.26 % (95 % CI [-0.36 %, -0.16 %], p-value < 0.001), compared to 0.015 % (95 % CI [-0.05 %, 0.08 %], p-value is 0.637) for 56 trials conducted outside of China. The difference of placebo effect between trials conducted in and outside China is -0.273 % (95 % CI [-0.42 %, -0.13 %], p-value is less than 0.001) while after excluding trials conducted in Japan, the difference is -0.203 % (95 % CI [-0.35 %, -0.06 %], p-value is 0.005). They are both statistically significant.

Conclusions: The meta-analysis in the article demonstrates that there is statistically significant difference in the HbA1c response in the placebo arm of DPP-4 inhibitor clinical trials conducted in China compared to other countries. This differential HbA1c response in the placebo arm should be taken into consideration by both experimenters and medical decision makers when future DPP-4 studies are conducted in China.

Keywords: Dipeptidyl peptidase-4 inhibitor, Diabetes mellitus, T2DM, Differential HbA1c response, Meta-analysis

Abbreviations: CFDA, China food and drug administration; DPP-4, Dipeptidyl peptidase-4; EU, European union; FDA, Food and drug administration; HbA1c, Glycosylated hemoglobin; T2DM, Type 2 diabetes mellitus
Background
Diabetes has become one of the most threatening non-infectious diseases. The prevention and treatment of diabetes is very important in China because China may have become a country with the largest number of diabetes patients. Most of these patients have type 2 diabetes mellitus (T2DM) [1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antihyperglycemic agents which has been proved to be better than some traditional treatments in many aspects [2–4]. The Guideline of Prevention and Treatment for T2DM in China [5] published by Chinese Diabetes Society places sitagliptin (FDA approved in 2009, marketed by Merck & Co. as Januvia), saxagliptin (FDA approved in 2009, CFDA approved in 2011, marketed by Bristol-Myers Squibb as Onglyza), vildagliptin (EU approved in 2007, CFDA approved in 2011, marketed by Novartis as Galvus), linagliptin (FDA approved in 2011, CFDA approved in 2013, marketed by Eli Lilly Co and Boehringer Ingelheim as Trajenta), alogliptin (FDA approved in 2013, CFDA approved in 2013, marketed by Takeda Pharmaceutical Company as Nesina).

Trials included in this meta-analysis met the following criteria: (1) Only randomized placebo controlled phase III clinical trials are included, (2) DPP-4 inhibitor as monotherapy or combination therapy is compared with placebo, (3) patients should be treated for at least 12 weeks, (4) HbA1c is the primary endpoint, (5) the trials were conducted in China with independent results of Chinese patients or conducted outside China without Chinese patients.

Methods
Search strategy and inclusion criteria
We searched EMBASE, PubMed, Google Scholar, ClinicalTrials.gov and PharmaProject for phase III placebo-control clinical trials of DPP-4 inhibitors in T2DM until March 2016. The key words for searching were sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin, Dipeptidyl peptidase-4 inhibitor and DPP-4. The publications of these trials came from EMBASE, PubMed, and Google. We also included studies from other countries and compared those conducted in China to those conducted in other countries.

Consequently, there is a critical need to investigate the differential HbA1c response in the placebo arm in trials conducted in China. To serve this need, we did a meta-analysis to investigate HbA1c response in the placebo arm in phase III placebo-control clinical trials of DPP-4 inhibitors. We concentrated on the HbA1c response in the placebo arm in trials conducted in China. We also included studies from other countries and compared those conducted in China to those conducted in other countries.

Statistical analysis
The package Metafor [8] in R was used to conduct statistical analysis for the HbA1c response in the placebo arm. This package consists of a collection of functions that allow the user to fit fixed-, random-, and mixed-effects models and to carry out meta-regression analysis. Weighted Mean change and 95 % confidence interval for changes from baseline in HbA1c in the placebo control groups were calculated. For studies in China, unless there was heterogeneity, we would use a fixed-effects model. Otherwise a random-effects model would be used. When comparing trials in China with those outside China, a mixed-effects model was performed. We use I^2 to determine heterogeneity [9] and leave-one-out to perform sensitivity analysis. Publication bias was examined by Egger’s regression test [10].

Results
Characteristics of studies
A total of 1632 papers and 217 trials were identified. After careful review, 10 studies [6, 11–19] conducted in China were included among which there were 3 unpublished trials [12, 13, 17]. In addition, 56 studies [20–75]
conducted outside China were included. Most of these trials including patients coming from different countries, while there were 17 trials [59–75] involving only Japanese patients. There were a total of 8303 participants (mean age 56, male 57 %) in placebo groups. Search results are summarized in Fig. 1.

The summarized information on the included studies is shown in Tables 1 and 2. Table 1 displays the information of studies conducted on Chinese patients in China. There are 4 trials for Sitagliptin, 3 trials for Vildagliptin, 2 trials for Linagliptin and 1 trial for Alogliptin. A total of 1634 patients with T2DM in the placebo groups were included. Their average age is between 50 and 60 while the average durations of diabetes are quite different. Average baselines of HbA1c are above 8 %. The treatment time of most studies is 24 weeks while Mohan [14] has 18 weeks and NCT01289119 [17] has 16 weeks. Besides, NCT01076088 [12] and NCT01289119 [17] both have 3 placebo groups.

Table 2 shows the 56 trials conducted on non-Chinese patients outside China. There are 21 trials for Sitagliptin, 13 trials for Vildagliptin, 9 trials for Linagliptin, 8 trials for Alogliptin and 5 trials for Saxagliptin. A total of 6669 patients with T2DM in the placebo groups were included. There is no significant difference in average age between patients in Tables 1 and 2, respectively, whereas the Japanese patients seem a little older than others. As for the duration of diabetes, patients in studies using insulin as the combination therapy suffered longer than others. The baselines of HbA1c range from 7.30 % to 9.30 %, and the variation is greater than those in Table 1. All the trials conducted in Japan treated patients for 12 weeks except Kadowaki 2013, and the treatment duration of most other studies in Table 2 is 24 weeks.

**Differential HbA1c response in the placebo arm**

We analyzed the placebo effect in all the trials, focusing on HbA1c change from baseline in controlled groups. Generally, placebo should not have a significant effect on HbA1c, even if there was combination therapy. The general HbA1c change from baseline in placebo controlled groups should be close to 0. However, it has been observed that there is a high placebo effect in some trials conducted in China [6]. We focused on HbA1c change...
from baseline in placebo controlled groups in trials conducted in China. We first summarized the HbA1c response in the placebo arm in trials conducted in China and then made a comparison to those conducted outside China.

Among 10 randomized placebo-controlled phase III clinical trials of DPP-4 inhibitors conducted in patients with T2DM in China, NCT01076088 [12] and NCT01177384 [13] have 3 placebo controlled groups with different combination therapy respectively. Thus totally 14 groups were included in the meta-analysis. Since there was substantial heterogeneity, random-effects model was performed. The weighted mean change from baseline was calculated and forest plot was drawn. Results are shown in Fig. 2. The results show that HbA1c is declined by 0.42 % with a \( p \)-value less than 0.001 in the placebo arm of randomized placebo controlled phase III clinical trials of DPP-4 inhibitors conducted in patients with T2DM in China. The 95 % confidence interval is (-0.66 %, -0.18 %).

We noted that the heterogeneity index \( I^2 \) of this model is significantly large. Thus we performed a leave-one-out sensitivity analysis to detect the influence of each study. Each time we left one group out, then fitted the same model. We got the summary estimates and \( I^2 \) of 14 models with results shown in Fig. 3. We found that the estimates of models that left out NCT01076088-2 [12] or NCT01076088-3 [12] are significant different from those in the full model that included all the 14 groups. The other groups show less heterogeneity. In addition, from Fig. 2, we see that the placebo effects of NCT01076088-2 [12] and NCT01076088-3 [12] are much higher than others, both larger than 1 %. In these two groups, metformin was used as combination therapy, patients’ baseline HbA1c were higher than average, and there were no information about the duration of diabetes. These might cause the significant difference in HbA1c decline between the two studies and others.

To decrease the heterogeneity, we further performed a random-effect model excluding these two groups. The weighted mean change from baseline was calculated and a forest plot was drawn. Results are shown in Fig. 4. In this model, \( I^2 \) declines to 71.63 %. We also performed a leave-one-out sensitivity analysis on this model. While leaving out some studies would decrease \( I^2 \), the estimates wouldn’t change much. The results based on the model excluding NCT01076088-2 [12] and NCT01076088-3 [12] indicate that, HbA1c in placebo controlled groups declined by 0.26 % with 95 % confidence interval being (-0.36 %, -0.16 %) and \( p \)-value less than 0.001 (Fig. 4). Egger’s regression test shows there is no publication bias (\( p \)-value is 0.802).

Table 1 Trials conducted in China

| Study ID         | Location | Drug        | Combination therapy       | Participants in placebo groups, N | Average age, years | Gender, male, % | Duration of diabetes, years | Baseline HbA1c, % | Change of HbA1c in placebo groups, % | Duration, weeks | Jadad score |
|------------------|----------|-------------|---------------------------|----------------------------------|--------------------|----------------|-------------------------------|----------------|--------------------------------------|----------------|------------|
| Yang [11]        | China    | Sitagliptin | Metformin                 | 198                              | 55                 | 55             | 7.30                          | 8.50           | -0.14                                | 24             | 5          |
| NCT01076088 [12] | China    | Sitagliptin | None                      | 127                              | 40                 | 68             | /                            | 8.97           | -0.59                                | 24             | /          |
|                  |          |             | Metformin                 | 126                              | 57                 | 55             |                              | 8.69           | -1.29                                |                |            |
|                  |          |             | Metformin                 | 124                              | 49                 | 60             |                              | 8.67           | -1.56                                |                |            |
| NCT01177384 [13] | China    | Sitagliptin | Acarbose                  | 189                              | 57                 | 51             | /                            | 8.08           | -0.14                                | 24             | /          |
| Mohan [14]       | China    | Sitagliptin | /                         | 82                               | 51                 | 60             | 1.70                          | 8.60           | -0.20                                | 18             | 5          |
| Pan [6]          | China    | Vildagliptin | Metformin                 | 144                              | 54                 | 46             | 5.15                          | 8.01           | -0.54                                | 24             | 3          |
| Yang [15]        | China    | Vildagliptin | Glimepiride               | 136                              | 59                 | 58             | 6.90                          | 8.70           | -0.20                                | 24             | 4          |
| Zeng [16]        | China    | Linagliptin | Metformin & sulphonylurea | 48                               | 57                 | 52             | >5                            | 8.13           | 0.08                                 | 24             | 3          |
| NCT01289119 [17] | China    | Alogliptin  | None                      | 93                               | 53                 | 58             | 2.12                          | /              | -0.42                                | 16             | /          |
|                  |          |             | Metformin                 | 98                               | 53                 | 49             | 5.33                          | -0.22          |                                      |                |            |
|                  |          |             | Pioglitazone              | 63                               | 52                 | 62             | 4.85                          | -0.25          |                                      |                |            |
| Chen [18]        | China    | Linagliptin | /                         | 88                               | 54                 | 59             | /                            | 8.09           | -0.25                                | 24             | 4          |
| Ning [19]        | China    | Vildagliptin | Insulin                   | 118                              | 58.5               | 55             | 11.4                          | 8.6            | -0.22                                | 24             | 5          |
| Study ID   | Location    | Drug          | Combination therapy | Participants in placebo groups, N | Average age, years | Gender, male, % | Duration of diabetes, years | Baseline HbA1c, % | Change of HbA1c in placebo groups, % | Duration, weeks | Jadad score |
|-----------|-------------|---------------|---------------------|----------------------------------|-------------------|----------------|---------------------------|----------------|-------------------------------------|----------------|-------------|
| Rosenstock [20] | non-China   | Alogliptin    | Insulin             | 130                              | 55                | 48             | 12.2                      | 9.30           | -0.13                               | 26             | 5           |
| Nauck [21]  | non-China   | Alogliptin    | Metformin           | 104                              | 56                | 48             | 6.0                      | 8.00           | -0.10                               | 26             | 5           |
| Raz [22]    | non-China   | Sitagliptin   | /                   | 103                              | 55                | 63             | 4.7                      | 8.00           | 0.12                                | 18             | 4           |
| Aschner [23] | non-China   | Sitagliptin   | /                   | 244                              | 54                | 51             | 4.6                      | 8.00           | 0.18                                | 24             | 4           |
| Hanefeld [24] | non-China   | Sitagliptin   | /                   | 111                              | 56                | 63             | 3.3                      | 7.60           | 0.12                                | 12             | 4           |
| Goldstein [25] | non-China   | Sitagliptin   | Metformin           | 176                              | 54                | 53             | 4.6                      | 8.70           | 0.17                                | 24             | 4           |
| Charbonnel [26] | non-China   | Sitagliptin   | Metformin           | 237                              | 55                | 60             | 6.6                      | 7.98           | -0.02                               | 24             | 4           |
| Raz [27]    | non-China   | Sitagliptin   | Metformin           | 94                               | 56                | 42             | 7.3                      | 9.10           | 0.00                                | 30             | 5           |
| Rosenstock [28] | non-China   | Sitagliptin   | Pioglitazone        | 178                              | 57                | 58             | 6.1                      | 8.02           | -0.15                               | 24             | 4           |
| Hermansen [29] | non-China   | Sitagliptin   | Glimepiride, Metformin | 219                         | 56                | 53             | 9.3                      | 8.34           | 0.28                                | 24             | 5           |
| Vilsbøll [30] | non-China   | Sitagliptin   | Insulin             | 319                              | 57                | 53             | 12.0                     | 8.60           | 0.00                                | 24             | 5           |
| Scott [31]  | non-China   | Sitagliptin   | /                   | 125                              | 55                | 62             | 4.8                      | 7.90           | 0.23                                | 12             | 5           |
| Scott [32]  | non-China   | Sitagliptin   | Metformin           | 92                               | 55                | 59             | 5.4                      | 7.70           | -0.22                               | 18             | 4           |
| Ristic [33] | non-China   | Vildagliptin  | /                   | 58                               | 55                | 57             | 2.3                      | 7.76           | -0.13                               | 12             | 3           |
| Dejager [34] | non-China   | Vildagliptin  | /                   | 94                               | 52                | 48             | 1.6                      | 8.40           | -0.30                               | 24             | 4           |
| Pi-Sunyer [35] | non-China   | Vildagliptin  | /                   | 92                               | 52                | 54             | 2.5                      | 8.50           | 0.00                                | 24             | 4           |
| Bosi [36]   | non-China   | Vildagliptin  | Metformin           | 130                              | 55                | 53             | 6.2                      | 8.30           | 0.20                                | 24             | 3           |
| Garber [37] | non-China   | Vildagliptin  | Pioglitazone        | 138                              | 55                | 51             | 4.8                      | 8.70           | -0.30                               | 24             | 4           |
| Garber [38] | non-China   | Vildagliptin  | Glimepiride         | 144                              | 58                | 58             | 7.8                      | 8.50           | 0.07                                | 24             | 5           |
| Fonseca [39] | non-China   | Vildagliptin  | Insulin             | 152                              | 59                | 55             | 14.9                     | 8.40           | -0.20                               | 24             | 4           |
| Defronzo [40] | non-China   | Saxagliptin   | Metformin           | 179                              | 55                | 54             | 6.7                      | 8.10           | 0.13                                | 24             | 4           |
| Del Prato [41] | non-China   | Linagliptin   | /                   | 167                              | 54                | 47             | /                        | 8.00           | 0.25                                | 24             | 4           |
| Taskinen [42] | non-China   | Linagliptin   | Metformin           | 177                              | 57                | 57             | /                        | 8.02           | 0.15                                | 24             | 4           |
| Moses [43]  | non-China   | Sitagliptin   | Sulfonlyurea, Metformin | 212                         | 55.4              | 46             | 8                        | 8.4            | -0.16                               | 24             | 5           |
| Laakso [44] | non-China   | Linagliptin   | Glimpiride          | 120                              | 66.6              | 63             | 4                        | 8.1            | -0.11                               | 12             | 3           |
| White [45]  | non-China   | Saxagliptin   | Metformin           | 84                               | 56.6              | 52.3           | 6.2                      | 7.97           | -0.22                               | 12             | 5           |
| Moses [46]  | non-China   | Saxagliptin   | Sulfonlyurea, Metformin | 127                         | 56.8              | 57.8           | /                        | 8.2            | -0.08                               | 24             | 4           |
| Bajaj [47]  | non-China   | Linagliptin   | Metformin, Pioglitazone | 89                           | 55.2              | 55.1           | /                        | 8.47           | -0.27                               | 24             | 4           |
| Fonseca [48] | non-China   | Sitagliptin   | Metformin, Pioglitazone | 153                         | 56.4              | 62.8           | 10.2                     | 8.6            | -0.4                                | 26             | 5           |
| Kothny [49] | non-China   | Vildagliptin  | Insulin             | 221                              | 59.1              | 52             | 13.2                     | 8.8            | -0.1                                | 24             | 4           |
| Dobs [50]   | non-China   | Sitagliptin   | Metformin, Osiglitazone | 88                           | 54.8              | 60             | 9.4                      | 8.7            | -0.3                                | 18             | 5           |
| Lewin [51]  | non-China   | Linagliptin   | Sulfonlyurea        | 82                               | 56.2              | 61.9           | /                        | 8.6            | -0.07                               | 18             | 4           |
| Study | Country | Treatment | Comparator | N  | Mean Baseline HbA1c (%) | Mean Baseline BMI (kg/m²) | Mean Change in HbA1c (%) | Mean Change in BMI (kg/m²) | Mean Days | Mean Doses |
|-------|---------|-----------|------------|----|-------------------------|---------------------------|-----------------------------|-----------------------------|-----------|------------|
| Barnett [52] | non-China | Linagliptin | / | 73 | 56.7 | 43.4 | / | 8.1 | 0.21 | 18 | 5 |
| Forst [53] | non-China | Linagliptin | Metformin | 70 | 60.1 | 62 | 6.2 | 8.4 | 0.24 | 12 | 4 |
| Nowicki [54] | non-China | Saxagliptin | / | 83 | 66.2 | 48.2 | 18.2 | 8.09 | -0.44 | 12 | 5 |
| Gomis [55] | non-China | Linagliptin | Pioglitazone | 128 | 57.1 | 65.4 | / | 8.58 | -0.56 | 24 | 4 |
| Hollander [56] | non-China | Saxagliptin | Thiazolidinedione | 180 | 54.1 | 46.2 | 5.1 | 8.2 | -0.3 | 24 | 4 |
| Pratley [57] | non-China | Alogliptin | Glyburide | 99 | 57.1 | 51.5 | 7.7 | 8 | 0.01 | 26 | 4 |
| Pratley [58] | non-China | Vildagliptin | / | 26 | 52.8 | 50 | 3.5 | 8.1 | 0 | 12 | 5 |
| Nonaka [59] | Japan | Sitagliptin | / | 76 | 55 | 66 | 4.1 | 7.70 | 0.41 | 12 | 5 |
| Kikuchi [60] | Japan | Vildagliptin | / | 20 | 62 | 55 | 7.2 | 7.30 | 0.28 | 12 | 4 |
| Iwamoto [61] | Japan | Sitagliptin | / | 73 | 60 | 69 | 6.4 | 7.74 | 0.28 | 12 | 4 |
| Kikuchi [62] | Japan | Vildagliptin | Glimepiride | 100 | 60 | 69 | 9.8 | 8.00 | -0.06 | 12 | 4 |
| Kaku [63] | Japan | Alogliptin | Pioglitazone | 115 | 60 | 66 | 6.7 | 7.92 | -0.19 | 12 | 4 |
| Kashwagi [64] | Japan | Sitagliptin | Pioglitazone | 68 | 59 | 72 | 7.6 | 8.00 | 0.40 | 12 | 5 |
| Seino [65] | Japan | Alogliptin | Voglibose | 75 | 62 | 64 | 7.5 | 8.12 | 0.04 | 12 | 5 |
| Kawamori [66] | Japan | Linagliptin | / | 80 | 60 | 71 | 5.0 | 7.95 | 0.63 | 12 | 4 |
| Seino [67] | Japan | Alogliptin | Metformin | 100 | 52 | 72 | 6.0 | 8.00 | 0.21 | 12 | 5 |
| Seino [68] | Japan | Alogliptin | Sulfonylurea | 103 | 60 | 69 | 9.4 | 8.62 | 0.35 | 12 | 4 |
| Kadawaki [69] | Japan | Sitagliptin | Metformin | 72 | 57 | 68 | 7.3 | 8.40 | 0.30 | 12 | 5 |
| Kaku [70] | Japan | Alogliptin | Insulin | 89 | 62 | 53 | 14.5 | 8.43 | -0.31 | 12 | 4 |
| Odawara [71] | Japan | Vildagliptin | Metformin | 70 | 58 | 69 | 7.0 | 8.00 | -0.10 | 12 | 4 |
| Hirose [72] | Japan | Vildagliptin | Insulin | 75 | 60.1 | 71.2 | 12.9 | 8.1 | -0.11 | 12 | 5 |
| Tajima [73] | Japan | Sitagliptin | Voglibose | 63 | 58.6 | 71.5 | / | 7.9 | 0.2 | 12 | 4 |
| Kadawaki [74] | Japan | Sitagliptin | Insulin | 128 | 60.2 | 58.4 | 14 | 8.9 | 0.3 | 16 | 4 |
| Tajima [75] | Japan | Sitagliptin | Glimepiride | 64 | 61 | 58.2 | 7.9 | 8.3 | 0.3 | 12 | 5 |
Considering minimizing the impact of heterogeneity in the analysis, the analysis based on the model excluding the two heterogeneous studies may be more reliable. Thus, for future reference, we may conclude that placebo decreases HbA1c by 0.26 % (95 % CI [-0.36 %, -0.16 %] and p-value less than 0.001) generally in trials conducted in Chinese patients in China (Fig. 4).

We compared trials conducted in China with those outside China using a mixed-effects model. Table 3 shows the analysis results. The model is fitted with location as a moderator. We treat location as a binary variable, 1 for China and 0 for non-China.

The intercept, 0.015 % (95 % CI [-0.05 %, 0.08 %], p-value is 0.637), shows that the HbA1c response in the placebo arm of trials conducted outside China (location = 0) is close to 0. The coefficient for location, -0.273 % (95 % CI [-0.42 %, -0.13 %], p-value is less than 0.001), shows a large difference of HbA1c response in the placebo arm between trials conducted in China (location = 1) and those outside China. The difference is statistically significant.

In addition, as trials conducted in Japan have shorter test duration and in some trials placebo significantly increased HbA1c, we performed another model treating Japan as a separate group. Table 4 shows the analysis results.
results. The model is fitted with location as a moderator, 1 for China, 2 for Japan and 0 for others.

This model shows that the HbA1c response in the placebo arm in trials conducted in countries except China and Japan was close to 0 (-0.055 with p-value 0.118). Trials conducted in Japan had a reverse placebo effect which means placebo increased HbA1c by 0.22 % (95 % CI [0.10 %, 0.34 %], p-value is less than 0.001). Finally, the model shows the difference of HbA1c response in the placebo arm between trials conducted in China and other countries except Japan is -0.203 % (95 % CI [-0.35 %, -0.06 %]) with a p-value of 0.005. The difference is also statistically significant.

**Discussion**

DPP-4 inhibitors are an important class of oral antihyperglycemic agents [2–4]. Until now five DPP-4 inhibitors, sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin, have been approved for marketing by CFDA. A large number of trials have been conducted in China determining the efficacy of these drugs in Chinese patients. For example, in a 24-week, randomized, double-blind, placebo-controlled study with 438 Chinese T2DM patients, Pan [6] discovered that the adjusted mean change in HbA1c at endpoint was $-1.05 \pm 0.08 \%$, $-0.92 \pm 0.08 \%$ and $-0.54 \pm 0.08 \%$ in patients receiving vildagliptin 50 mg bid, 50 mg qd and placebo, respectively. In this study, the 95 % confidence interval for the HbA1c response in the placebo arm is (-0.70, -0.38), indicating an HbA1 decline in the placebo arm. Similar HbA1 decline was discovered in a fair number of other trials in Chinese patients such as NCT01076088 [12] and NCT01289119 [17]. There are a few trials with the 95 % confidence interval of HbA1 in the placebo arm covering 0 such as (-0.28, 0) in Yang [11] and (-0.16, 0.32) in Zeng [16]. However, no trial has shown a significant HbA1c increase in the placebo arm in trials with Chinese patients. Therefore, there is a suspicion that there is an HbA1c decline in the placebo arm of DPP-4 inhibitor clinical trials conducted in China. Is that suspicion true? No one has addressed this question systematically yet. Therefore, in this article, we use a systematic meta-analysis approach to address this question.

The meta-analysis shows that, HbA1c in the placebo arm declined by 0.26 % (95 % CI [-0.36 %, -0.16 %]) with a p-value less than 0.001. Therefore, there is a suspicion that there is an HbA1c decline in the placebo arm of DPP-4 inhibitor clinical trials conducted in China. 

| Study ID   | Placebo-effect [95% CI] | Weight | Factor(location)1  |
|------------|-------------------------|--------|-------------------|
| Yeng 2012[11] | -0.14 ( -0.26 , 0.00 ) | 9.45%  | 0.031             |
| NCT01076088-1[12] | -0.59 ( -0.84 , -0.34 ) | 6.68%  | 0.031             |
| NCT01177308[13] | -0.14 ( -0.31 , 0.03 ) | 5.63%  | 0.031             |
| Mohan 2009[14] | -0.20 ( -0.38 , -0.02 ) | 8.35%  | 0.031             |
| Pan 2012[6] | -0.54 ( -0.70 , -0.38 ) | 9.13%  | 0.031             |
| Yang 2014[15] | -0.20 ( -0.40 , 0.00 ) | 8.05%  | 0.031             |
| Zeng 2013[16] | 0.08 ( -0.16 , 0.32 ) | 7.04%  | 0.031             |
| NCT01289119-1[17] | -0.42 ( -0.57 , -0.27 ) | 9.45%  | 0.031             |
| NCT01289119-2[17] | -0.22 ( -0.35 , -0.09 ) | 9.93%  | 0.031             |
| NCT01289119-3[17] | -0.25 ( -0.44 , -0.06 ) | 8.21%  | 0.031             |
| Chen 2015[18] | -0.26 ( -0.47 , -0.03 ) | 7.53%  | 0.031             |
| Ning 2016[19] | -0.22 ( -0.44 , 0.00 ) | 7.53%  | 0.031             |

**Table 3: Mixed-effects model 1 (k = 68)**

|                  | Standard error | z value | p value | Lower 95% confidence interval | Upper 95% confidence interval |
|------------------|----------------|---------|---------|------------------------------|-------------------------------|
| Intercept        | 0.015          | 0.031   | 0.472   | 0.637                        | -0.047                        | 0.076                         |
| Factor(location)1 | -0.273         | 0.076   | -3.612  | <-0.001                      | -0.421                        | -0.125                        |

The model is fitted with location as moderator. Location was regarded as binary variable, 1 for China and 0 for non-China.
the placebo effect of those conducted outside China is close to 0. The difference of HbA1c in the placebo arm between trials conducted in China and outside China is -0.273 % (95 % CI [-0.42 %, -0.13 %], p-value is less than 0.001). After excluding trials conducted in Japan, the difference is -0.203 % (95 % CI [-0.35 %, -0.06 %]) with a p-value of 0.005. They are both statistically significant. Therefore, after we investigated the placebo effect of randomized placebo controlled phase III clinical trials of DPP-4 inhibitors conducted in patients with T2DM in China, we concluded that there was statistically significant difference in response in the placebo arm between trials conducted in China and outside China. This difference of HbA1c decline in the placebo arm should be taken into account in future studies in China.

There may be various reasons for this high placebo effect. However, what these reasons exactly are is unknown. Although the investigation of these reasons is not the purpose in this article, we have the following two major guesses. First, the practical process of these trials could cause a bias. Most of the trials provided the participants the significant benefit to obtain more resource of medical care, esp. in China. Because of no established PCP system, low awareness of diabetes management, China has most diabetes patients in the world [5] but much lower health workers/patient ratio than Europe, USA and Japan [76]. Clinical trials could have obvious impact on management of diabetes, and thus cause better blood glucose control even in placebo arm. Second, Traditional Chinese Medicine (TCM) could play role. There is evidence that the use of some TCM herbs can reduce hyperglycemia [77]. Among these herbs many are used commonly in diet or drinks. Normally in study protocol, herbs in diet were not clearly inhibited. Other reasons may include life style and culture that are unique in China.

The results on the placebo effect on other countries may also provide values for future trials and medical interpretation. For example, clinical trials conducted in Japan had a statistically significant reverse placebo effect, which may be important information for conducting future DDP-4 trials as well as for interpreting trial results in Japan.

Conclusions
The meta-analysis in the article demonstrates that there are significant differences in response in the placebo group of DPP-4 trials conducted in China compared to those conducted outside of China. This difference may give some clue to why the efficacy of these drugs is less statistically significant in trials conducted in China. More importantly, this difference in response in the placebo group should be taken into account for future DDP-4 trials conducted in China. In addition, the difference in placebo should be carefully considered by medical decision makers when future DDP-4 studies are conducted in China.

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Availability of data and materials
Data used in this paper were collected from openly published papers and trials listed as references [6, 11–75].

Authors’ contributions
LH conducted the analysis and took a lead in drafting the manuscript; XDZ initiated the idea and supervised the analysis and writing, CS, SL, YT and ZL raised clinical motivation, gave clinical interpretation and revised the manuscript. LH and XDZ wrote the final manuscript. All authors read and approved the final manuscript.

Competing interests
Liu, Tu and Li are employees of Merck & Co., Inc.

Consent for publication
Not applicable.

Ethics approval and consent to participate
None. We collected data from openly published papers and trials.

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