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**Relationship of baseline HbA1c, HbA1c change, and HbA1c target of <7% with Insulin Analogues in Type 2 Diabetes: A meta-analysis of randomized controlled trials**

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# Relationship of baseline HbA1c, HbA1c change, and HbA1c target of <7% with Insulin Analogues in Type 2 Diabetes: A meta-analysis of randomized controlled trials

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## ABSTRACT

**Aim:** We performed a meta-analysis of randomized controlled trials (RCTs) with insulin analogues in type 2 diabetes utilizing a least-squared regression model in order to assess the relationship between baseline HbA1c, the magnitude of HbA1c decrease, and attainment of HbA1c target of <7%.

**Methods:** RCTs involving insulin regimens (basal, prandial, biphasic, and basal-bolus) were identified through electronic searches (MEDLINE, EMBASE, CINAHL, and The Cochrane Library) through September 2010. We included any study arm of RCTs if they were at least 12 weeks in duration, the number of patients in any arm was more than 30, and reported the baseline HbA1c and change from baseline HbA1c .

**Results:** We found 87 studies, with a total of 135 arms, and 38803 patients. The weighted  $R^2$  values for the overall analysis assessing the association between baseline HbA1c and absolute change in HbA1c or the proportion of patients at target were 0.485 ( $P < 0.001$ ) and 0.146 ( $P < 0.001$ ), respectively. Subanalyses of insulin regimens for the association between basal HbA1c and absolute decrease of HbA1c produced weighted  $R^2$  which were significant for all insulin regimens, with the highest association for basal-bolus ( $R^2 = 0.719$ ,  $P < 0.001$ ).

**Conclusions:** The strong positive relationship between baseline HbA1c and the magnitude of HbA1c change we found in RCTs using insulin analogues in type 2 diabetes should be considered when assessing the clinical efficacy of insulin therapies.

228 words

## What's known

- A haemoglobin A1c (HbA1c) concentration of 7% or less is recommended for most patients with type 2 diabetes to minimize the risk of vascular complications.
- Insulin analogues are increasingly used in the treatment of type 2 diabetes, with the aim to offer a better replication of the pattern of endogenous secretion of insulin.
- A positive relationship between baseline HbA1c levels and the magnitude of HbA1c decrease has been found for most glucose-lowering therapies.

## What's new

- We performed a meta-analysis of randomized controlled trials with insulin analogues in type 2 diabetes to assess the relationship between baseline HbA1c, the magnitude of HbA1c decrease, and attainment of HbA1c target of <7%.
- We included 87 studies with 38803 patients. We found that higher baseline HbA1c levels are associated with greater reduction in HbA1c and with a lower proportion of patients at target for the HbA1c <7%.
- These findings should be considered when assessing clinical efficacy of insulin therapies with insulin analogues derived from clinical trials.

## Introduction

The efficacy of any glucose-lowering therapies is currently based upon their ability to improve blood glucose control, which generally is assessed by the absolute reduction in haemoglobin A1c (HbA1c). However, a positive relationship between baseline HbA1c levels and the magnitude of HbA1c decrease has been found for most glucose-lowering therapies, pointing to a general phenomenon not linked to any specific drug or class (1-3). These findings may have important implications as both the FDA and EMA suggest consider baseline HbA1c as an adjustment factor in the assessment of agent efficacy (4,5).

Tight glycaemic control, to maintain a HbA1c concentration of 7% or less, is recommended for most patients with type 2 diabetes to minimize the risk of vascular complications (6). Although traditionally used as a final treatment option, insulin has been recently recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) to be introduced earlier for controlling hyperglycaemia in type 2 diabetes, after lifestyle changes and metformin fail to reach and/or maintain HbA1c of less than 7% (7). Insulin analogues are increasingly used in the treatment of human diabetes, with the aim to offer a better replication of the pattern of basal and postprandial endogenous secretion of insulin (8). Conversion of the insulin market to analogues, estimated to be 40-45% in 2005, has been projected to reach saturation within 2010 (9).

In this study, we performed a meta-analysis of randomized controlled trials (RCTs) with insulin analogues in type 2 diabetes utilizing a least-squared regression model in order to assess the relationship between baseline HbA1c, the magnitude of HbA1c decrease, and attainment of HbA1c target of <7%.

## METHODS

The present meta-analysis was conducted in accordance with guidelines established by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (10). Reports of

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2  
3 RCTs of insulin analogues in type 2 diabetes patients were identified through systematic literature  
4 search of MEDLINE, EMBASE, The Cochrane Library, and CINAHL through September 2010.  
5  
6 The main search concepts were type 2 diabetes, haemoglobin A1c, long-acting insulin analogues,  
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8 short-acting insulin analogues, biphasic insulin analogues, glargine, detemir, neutral protamine  
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10 lispro, lispro, aspart, glulisine, randomized controlled trials, clinical trials. We also reviewed  
11  
12 reference lists of included articles, the U.S. Food and Drug Administration and European Medicines  
13  
14 Agency Web sites for the insulin analogues, and Web sites of public registries of clinical trials  
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16 (ClinicalTrials.gov and ClinicalStudyResults.org).  
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## 22 **Study selection**

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24 We included any study arm of randomized controlled trials if: a) patients >18 years old with a  
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26 diagnosis of type 2 diabetes, as defined by criteria current at the time of the trial, were included; b)  
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28 different insulin regimens (basal, biphasic, prandial or basal-bolus) using insulin analogues were  
29  
30 evaluated; and c) baseline HbA1c and change from baseline HbA1c were reported. Trials were  
31  
32 rejected if the intervention time was < 12 weeks, or the number of patients in any arm was less than  
33  
34 30 patients. Clinical trials addressing patients with Type 1 diabetes were excluded. We included  
35  
36 crossover trials with at least 12 weeks of follow-up before and after the crossover phase. The search  
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38 had no language restriction; we excluded reviews, editorials, comments, letters, and abstracts. Two  
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40 investigators (D.G. and K.E.) identified relevant publications and abstracted the data, and any  
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42 disagreements were resolved by consensus. Data were abstracted and independently checked for  
43  
44 accuracy prior to statistical analyses.  
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## 50 **Insulin regimens**

51  
52 We considered four insulin regimens: basal insulin consisted of long-acting insulin analogues  
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54 (glargine, detemir, and lispro NPL); biphasic insulin consisted of premixed insulin analogues (lispro  
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56 25/75, lispro 50/50, aspart 30/70, aspart 50/50, aspart 70/30, the numbers denote the percentage of  
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58 the rapid-acting to the long-acting component, respectively); prandial insulin consisted of short-  
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3 acting insulin analogues (lispro, aspart, glulisine); and basal-bolus insulin consisted of any  
4  
5 combination of prandial and basal insulin analogues.  
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## 8 **Data synthesis and analyses**

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10 The proportion of patients with HbA1c <7% across the selected trials was computed as Pooled  
11 OR (POR) with 95% CI, as previously described (11). In brief, we transformed the proportion of  
12  
13 patients with HbA1c <7% at the end of treatment into a quantity suitable for the usual fixed and  
14  
15 random effects summaries (the Freeman-Tukey variant of the arcsine square root transformed  
16  
17 proportion) (12). The pooled proportion is calculated as back-transformation of the weighted mean  
18  
19 of the transformed proportions, using inverse arcsine variance weights for the fixed effects model  
20  
21 and DerSimonian-Laird weight for the random effects model (13).  
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27 In 32 trials (39 arms and 5559 patients), which qualified for inclusion/exclusion criteria, the  
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29 proportion of patients with HbA1c <7% at the end of treatment was not reported. We used the  
30  
31 available information from the 55 trials (96 arms and 33244 patients) that reported the proportion of  
32  
33 patients with HbA1c <7% for developing an algorithm for the estimate of the proportion of patients  
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35 with HbA1c <7% (p) starting from the mean value of HbA1c reported at the end of treatment. The  
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37 algorithm was a linear regression model relating the logit of the success rate ( $\log(p/(1-p))$ ) with the  
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39 HbA1c at the end of the treatment. Following there is the resulting equation to predict the logit of  
40  
41 the success rate:  $\log(p/1-p) = 11.68167-164.3119 \times \text{HbA1c-end}$ . This equation explained the 88% of  
42  
43 the variability between studies, and just little deviance between observed and predicted success  
44  
45 rates were reported. The success rate (p) was then given by simple mathematical transformations.  
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51 The relationships between baseline HbA1c and change from baseline HbA1c, and  
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53 between baseline HbA1c and attainment of the HbA1c target of <7% were analyzed by a  
54  
55 weighted least-squared regression model using the S-PLUS 6.1 for Windows (Insightful  
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57 Corp., Seattle, WA, USA), and sas version 9.2 for Windows (SAS Institute, Cary, NC, USA).  
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The weight was computed as the inverse of the variance.



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3 The following subanalyses also were conducted: 1) trial arms with basal insulin (57 arms with  
4 21615 patients assessing the long-acting insulin analogues glargine, detemir, and lispro NPL); 2)  
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6 trial arms with biphasic insulin (49 arms with 11624 patients assessing the premixed insulin  
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8 analogues lispro 25/75, lispro 50/50, aspart 30/70, aspart 50/50, aspart 70/30); 3) trial arms with  
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10 prandial insulin (13 arms with 2597 patients assessing the short-acting insulin analogues lispro,  
11  
12 aspart, and glulisine); and 4) trial arms with basal-bolus insulin (16 arms with 2967 patients  
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14 assessing any combination of prandial and basal insulin analogues.  
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20 Publication bias in these meta-analyses was assessed by funnel plot analyses, which revealed  
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22 symmetrical relationships around mean change in HbA1c (data not shown).  
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## 25 RESULTS

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27 The process of selecting the RCTs utilized in the final analyses from the 2700 citations originally  
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29 identified is described in Fig. 1. We found 87 studies (14-100), with a total of 135 arms, that  
30  
31 satisfied the inclusion/exclusion criteria. Most trials were multinational and sponsored by industry.  
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33 All studies were randomized controlled trials (Table 1): among these, most were parallel group and  
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35 8 were crossover. All studies were of open-label design except one. Trial duration ranged from 12  
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37 to 134 weeks. The trials enrolled a total of 38803 patients (range, 41 to 2493 patients per arm);  
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39 baseline HbA1c ranged from 7.2% to 10.6%.  
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43 The baseline HbA1c level, the decrement of HbA1c after treatment, and the proportion of patients  
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45 at target with HbA1c <7% for the overall population and for each specific insulin regimen are  
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47 reported in Table 2. Also reported in Table 2 are the relation between basal HbA1c and the  
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49 decrement of HbA1c, and between basal HbA1c and proportion of patients at target. The median  
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51 HbA1c level ranged from 8.35% with basal-bolus insulin to 9.1% with biphasic insulin; the  
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53 decrement of HbA1c ranged from a median value of 1.32% with basal insulin to 1.4% with biphasic  
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55 or prandial insulin; and the proportion of patients at target ranged from 35% with biphasic insulin to  
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57 51% with basal-bolus insulin.  
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3 The weighted  $R^2$  values for the overall analysis assessing the association between baseline  
4 HbA1c and absolute change in HbA1c (Fig 1) or the proportion of patients at target (Fig 2) were  
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6 0.485 ( $P < 0.001$ ) and 0.146 ( $P < 0.001$ ), respectively.  
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10 Subanalyses of different insulin regimens were also carried out (Table 2). Subanalyses of insulin  
11 regimens for the association between basal HbA1c and absolute decrease of HbA1c produced  
12 weighted  $R^2$  which were significant for all insulin regimens, with the highest association for basal-  
13 bolus (0.719,  $P < 0.001$ ). On the contrary, subanalysis of insulin regimens for the association  
14 between basal HbA1c and proportion of patients at target produced weighted  $R^2$  which were  
15 significant for basal (0.195,  $P < 0.001$ ) and biphasic insulin (0.076,  $P = 0.037$ ), but not significant  
16 for prandial (0.127,  $P = 0.126$ ) or basal-bolus insulin (0.000,  $P = 0.526$ ).  
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## 29 DISCUSSION

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31 The current meta-analysis demonstrates that higher baseline HbA1c levels are associated with  
32 greater reduction in HbA1c in clinical trials using different insulin regimens with insulin analogues  
33 in type 2 diabetes. Moreover, higher baseline HbA1c levels are also associated with a lower  
34 proportion of patients at target for the HbA1c  $< 7\%$ . This last negative association, however, was of  
35 lesser significance and not present for all the insulin regimens. To our knowledge, this is the first  
36 comprehensive analysis assessing the association between baseline HbA1c level and two HbA1c  
37 outcomes, namely the decrease of HbA1c and the proportion of patients at HbA1c target, currently  
38 adopted in clinical trials for evaluating the efficacy of insulin analogues in type 2 diabetes.  
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50 Recruitment to a clinical trial can produce a clinically useful improvement in glycaemic control,  
51 especially in those with relatively poor control at study outset (101). This finding well describes the  
52 positive relationship between baseline HbA1c levels and the magnitude of HbA1c change. The  
53 weighted  $R^2$  values for the analysis assessing the association between baseline HbA1c and absolute  
54 change in HbA1c in the all 135 arms was highly significant (0.485,  $P < 0.001$ ), and of greater  
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3 magnitude that that previously reported for other glucose-lowering therapies (1-3), which ranged  
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5 from  $R^2 = 0.18$  (1) to  $R^2 = 0.31$  (2). The difference between our results and those reported earlier  
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7 for other noninsulin, glucose-lowering therapies may be due to greater biological potency of insulin,  
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9 which remains the most effective of diabetes medications in lowering glycaemia. Insulin can, when  
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11 used in adequate doses, decrease any level of elevated HbA1c to, or close to, the therapeutic goal.  
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13 Unlike the other blood glucose-lowering medications, there is no maximum dose of insulin beyond  
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15 which a therapeutic effect will not occur (7). Although it may appear obvious that the closer the  
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17 baseline HbA1c is to the target, the higher the probability to reach the target, we found evidence for  
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19 a mild association between baseline HbA1c level and attainment of the target in all 135 arms ( $R^2 =$   
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26 0.146).

27 This study has limitations. Many trials were of low methodological quality, but this is expected  
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29 when the double-blind masking is not possible as for insulin trials. Moreover, about 15% of the  
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31 included arms (21/135) reported the effect of therapies for period greater than 26 weeks, which  
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33 makes unclear whether the HbA1c outcomes can be replicated during longer treatments. Finally, the  
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35 influence of a publication bias cannot be entirely excluded as studies with positive results are more  
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37 likely to be published, resulting in an overestimate of the benefit of insulin analogues on HbA1c  
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39 reduction. This study has also strengths as it was restricted to RCTs that met predetermined  
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41 methodological criteria: it focused on the effect of insulin regimens with insulin analogues which  
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43 may be clinical relevant given the increasing number of patients with type 2 diabetes that are using  
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45 insulin, either alone or in combination with oral antidiabetic drugs (102); it was conducted using  
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47 weighted data from prospective cohort studies; lastly, the high number of RCTs included (87 RCTs  
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49 with 135 arms) and the huge number of patients investigated (38 803), makes unlikely the  
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51 possibility that even missed (non published) data may alter the associations herein reported.  
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57 In conclusion, our analysis of 38 804 patients with type 2 diabetes using insulin analogues  
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59 demonstrate a strong positive relationship between baseline HbA1c and the magnitude of HbA1c  
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3 change, and a smaller one between baseline HbA1c and the proportion of patients at the HbA1c  
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5 target of <7%. The findings herein reported should be considered when assessing clinical efficacy  
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7 of insulin therapies with insulin analogues derived from clinical trials. Future trials should consider  
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9 and correct for these variables (starting HbA1c value and HbA1c decrease) in the interpretation of  
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11 data.  
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10 Figure 1. Systematic review flow diagram; n=number of trial reports.  
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14  
15 Fig 2. Relationship between baseline HbA1c and change in HbA1c with insulin analogues in type 2  
16 diabetes. The size of each circle in the figure represents the weighted mean in an individual arm of  
17 randomized controlled trials.  
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25 Fig 3. Relationship between baseline HbA1c and achievement of HbA1c target of <7% with insulin  
26 analogues in type 2 diabetes. The size of each circle in the figure represents the weighted mean in  
27 an individual arm of randomized controlled trials.  
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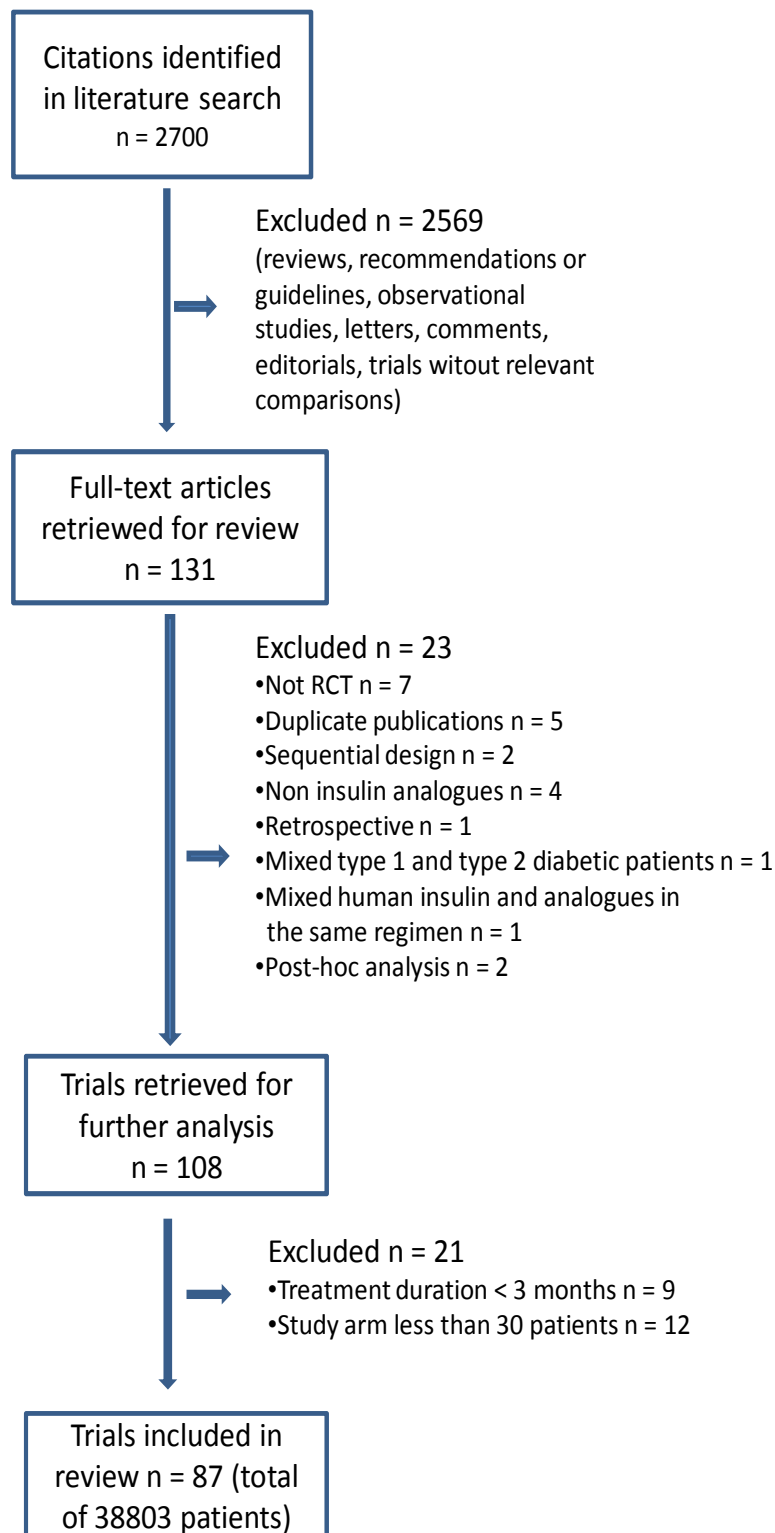


Figure 1

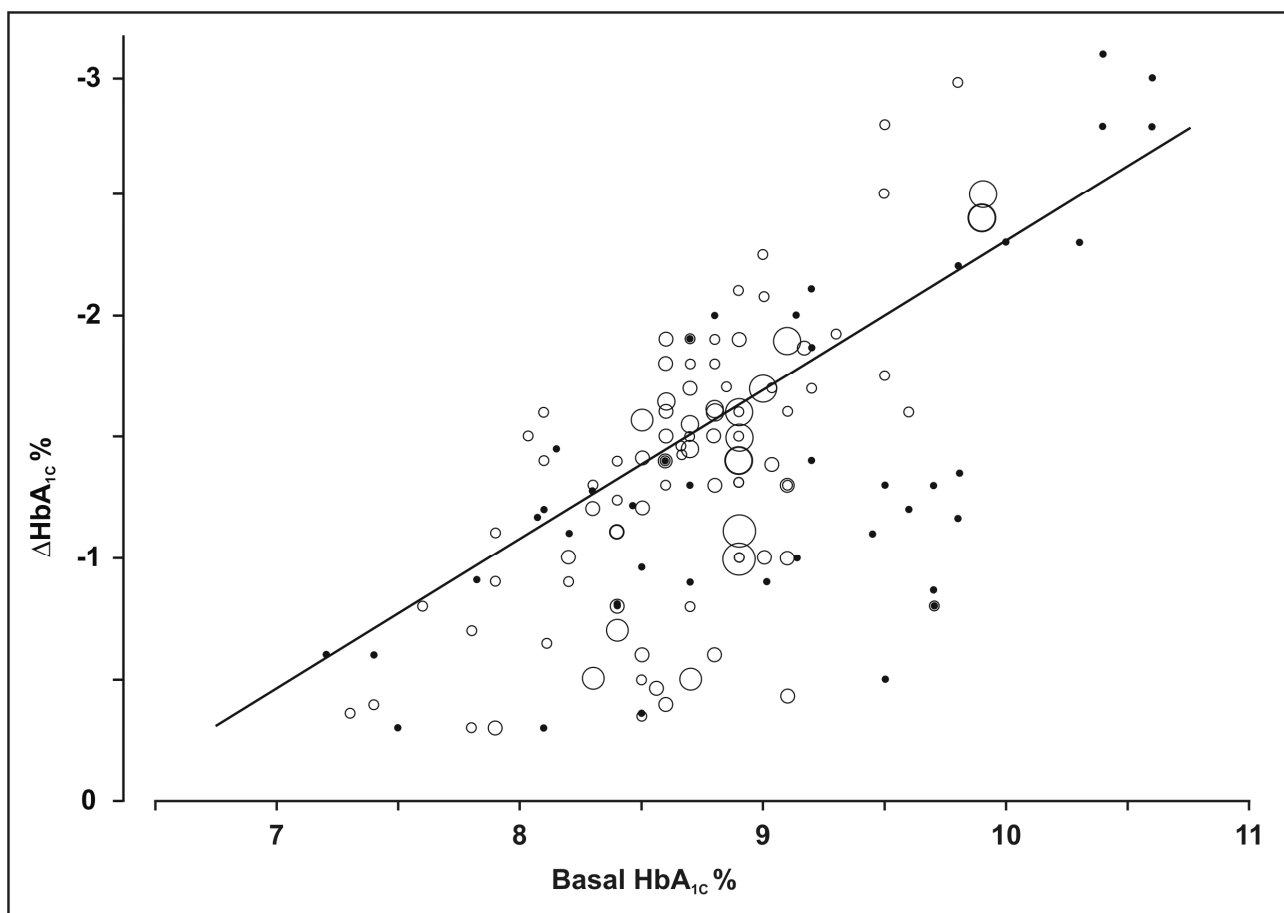


Figure 2

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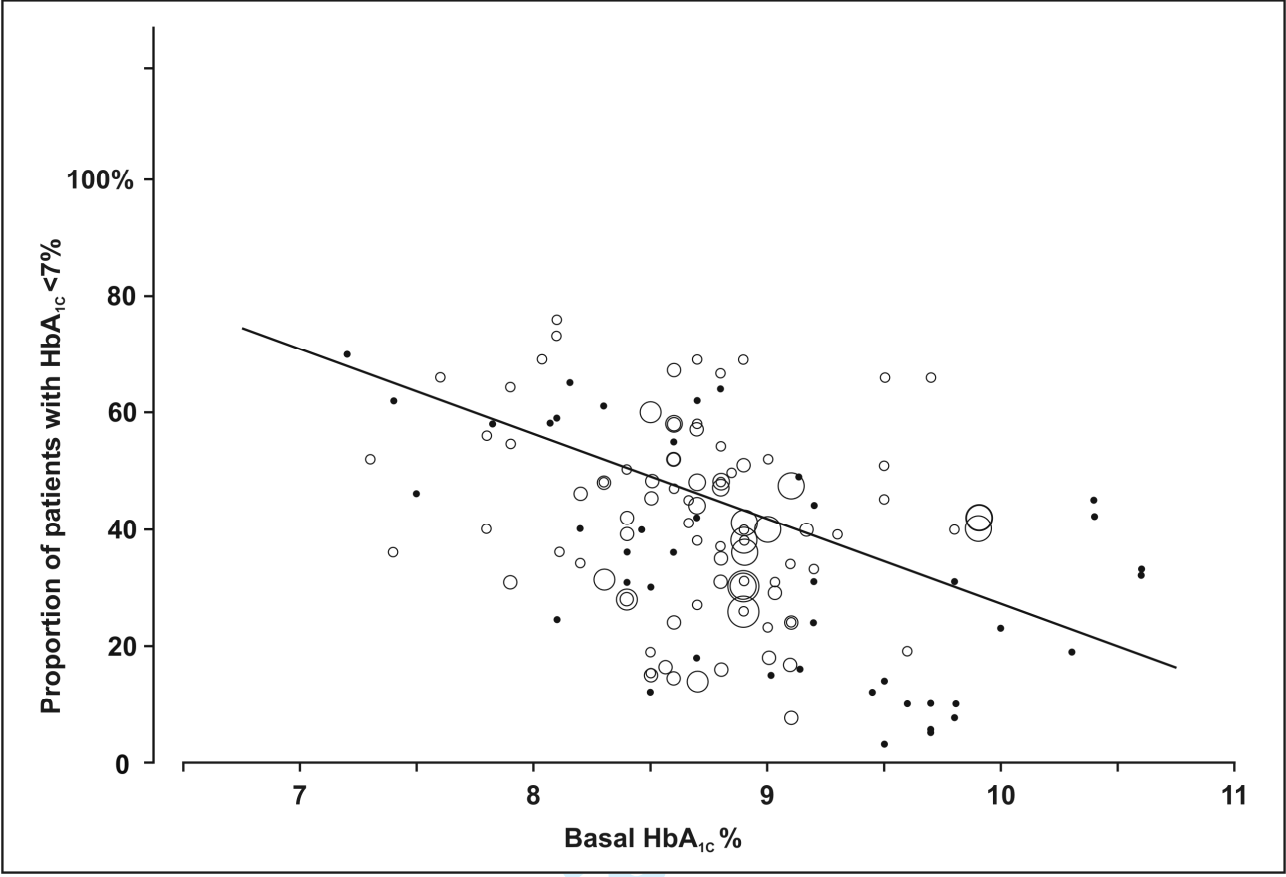


Figure 3

Table 1. Characteristics of the Studies Included in the Systematic Review.

Studies (author, year, reference)	No	Analogue	Lenght wk	HbA1c basal (%)	HbA1c change (%)	HbA1c <7% (%)	R vs C
<b>Basal insulin: 44 RCTs, 57 arms</b>							
Riddle, 2003 <sup>14</sup>	367	Glargine	24	8.6	-1.64	58	R
Malone, 2004 <sup>15</sup>	67	Glargine	16	8.7	-0.9	18	R
Raskin, 2005 <sup>16</sup>	114	Glargine	24	9.8	-2.39	40	R
Heine, 2005 <sup>17</sup>	260	Glargine	24	8.3	-1.2	48	R
Janka, 2005 <sup>18</sup>	177	Glargine	24	8.85	-1.7	49	R
Malone, 2005 <sup>19</sup>	97	Glargine	16	8.5	-0.36	12	R
Davies, 2005 <sup>20</sup>	2493	Glargine	24	8.9	-1.0	26	R
Davies, 2005 <sup>20</sup>	2468	Glargine	24	9.9	-1.1	30	R
Kann, 2006 <sup>21</sup>	127	Glargine	24	8.9	-1.0	26	R
Jacobson, 2006 <sup>22</sup>	59	Glargine	16	9.2	-1.86	31	R
Kazda, 2006 <sup>23</sup>	53	Glargine	16	8.1	-0.3	24.5	R
Kennedy, 2006 <sup>24</sup>	1491	Glargine	24	8.9	-1.4	30	R
Kennedy, 2006 <sup>24</sup>	1363	Glargine	24	8.9	-1.4	36	R
Kennedy, 2006 <sup>24</sup>	1501	Glargine	24	8.9	-1.5	38	R
Kennedy, 2006 <sup>24</sup>	1366	Glargine	24	8.9	-1.6	41	R
Hermansen, 2006 <sup>25</sup>	227	Detemir	24	8.6	-1.8	70	R
Rosenstock, 2006 <sup>26</sup>	104	Glargine	24	8.8	-1.68	48	R
Gernstein, 2006 <sup>27</sup>	206	Glargine	24	8.6	-1.6	58	R
Standl, 2006 <sup>28</sup>	308	Glargine	24	8.8	-1.62	48	R
Standl, 2006 <sup>28</sup>	316	Glargine	24	8.8	-1.6	47	R
Holman, 2007 <sup>29</sup>	234	Detemir	52	8.4	-0.8	28	R
Robbins, 2007 <sup>30</sup>	158	Glargine	24	7.8	-0.3	40	R
Barnett, 2007 <sup>31</sup>	138	Glargine	16	8.9	-1.32	40	R
Esposito, 2008 <sup>32</sup>	55	Glargine	36	8.8	-2.0	64	R
Esposito, 2008 <sup>32</sup>	55	Lispro NPL	36	8.7	-1.9	62	R
Bretzel, 2008 <sup>33</sup>	204	Glargine	48	8.7	-1.7	57	R
Rosenstock, 2008 <sup>34</sup>	248	Detemir	52	8.6	-1.4	52	R
Rosenstock, 2008 <sup>34</sup>	259	Glargine	52	8.6	-1.5	52	R
Buse, 2009 <sup>35</sup>	1046	Glargine	24	9.0	-1.7	40	R
Raz, 2009 <sup>36</sup>	558	Glargine	134	8.3	-0.5	31	R
Russell-Jones, 2009 <sup>37</sup>	232	Glargine	24	8.2	-1.0	46	R
Bicklé, 2009 <sup>38</sup>	103	Glargine	36	7.6	-0.8	66	R
Blonde, 2009 <sup>39</sup>	121	Detemir	20	7.9	-1.1	64	R
Blonde, 2009 <sup>39</sup>	122	Detemir	20	7.9	-0.9	54	R
Rosenstock, 2009 <sup>40</sup>	217	Glargine	24	8.5	-0.6	15	R



1								
2								
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4	Strojek, 2009 <sup>41</sup>	232	Glargine	24	8.5	-1.2	46	R
5	Fogelfeld, 2009 <sup>42</sup>	223	Lispro NPL	24	8.8	-1.5	35	R
6	Fogelfeld, 2009 <sup>42</sup>	219	Detemir	24	8.8	-1.3	31	R
7								
8	Heise, 2010 <sup>43</sup>	122	Glargine	26	8.6	-1.4	55	R
9								
10	Kalra, 2010 <sup>44</sup>	79	Glargine	26	8.4	-0.8	36	R
11	Swinnen, 2010 <sup>45</sup>	478	Glargine	24	8.7	-1.45	44	R
12	Swinnen, 2010 <sup>45</sup>	486	Detemir	24	8.7	-1.54	48	R
13								
14	Diamant, 2010 <sup>46</sup>	223	Glargine	26	8.3	-1.3	48	R
15	Strojek, 2010 <sup>47</sup>	235	Lispro NPL	24	8.67	-1.46	43.8	R
16	Strojek, 2010 <sup>47</sup>	236	Glargine	24	8.67	-1.41	41	R
17								
18	Yki-Yarvinen, 2000 <sup>48</sup>	213	Glargine	52	9,1	-0.44	7.5	C
19								
20	Rosenstock, 2001 <sup>49</sup>	259	Glargine	28	8.6	-0.4	14.5	C
21								
22	Massi-Benedetti, 2003 <sup>50</sup>	235	Glargine	52	8.56	-0.46	17	C
23	Fritsche, 2003 <sup>51</sup>	236	Glargine	24	9.1	-1.3	24	C
24	Fritsche, 2003 <sup>51</sup>	227	Glargine	24	9.1	-1.0	16.5	C
25								
26	Eliashewitz, 2006 <sup>52</sup>	231	Glargine	24	9.03	-1.38	29	C
27	Philis-Tsimikas, 2006 <sup>53</sup>	168	Detemir	20	9.1	-1.6	34,5	C
28	Philis-Tsimikas, 2006 <sup>53</sup>	170	Detemir	20	8.9	-1.5	39	C
29								
30	Yki-Jarvinen, 2006 <sup>54</sup>	55	Glargine	36	9.13	-2.0	49	C
31								
32	Yki-Jarvinen, 2007 <sup>55</sup>	121	Glargine	24	8.7	-1.8	58.5	C
33	Pan, 2007 <sup>56</sup>	220	Glargine	24	9.02	-1.0	18	C
34	Bunck, 2009 <sup>57</sup>	33	Glargine	52	7.4	-0.6	62	C
35								
36								
37	<b>Biphasic insulin: 37 RCTs, 49 arms</b>							
38								
39	Malone, 2003 <sup>58</sup>	296	Lispro 25/75	16	9.17	-1.87	40	R
40	Malone, 2004 <sup>15</sup>	67	Lispro 25/75	16	8.7	-1.3	42	R
41	Raskin, 2005 <sup>16</sup>	108	BIAspart 30/70	24	9.7	-1.8	66	R
42								
43	Malone, 2005 <sup>19</sup>	97	Lispro 25/75	16	8.5	-0.96	30	R
44								
45	Kann, 2006 <sup>21</sup>	128	BIAspart 30/70	24	9.2	-1.7	33	R
46	Jacober, 2006 <sup>22</sup>	59	Lispro50 + Lispro25	16	9.2	-2.12	44	R
47								
48	Kazda, 2006 <sup>23</sup>	54	Lispro 50/50	24	8.1	-1.2	59	R
49	Holman, 2007 <sup>29</sup>	235	BIAspart 30/70	52	8.4	-1.1	42	R
50								
51	Ushakova, 2007 <sup>59</sup>	100	BIAspart 30/70	16	10.4	-3.1	45	R
52	Ushakova, 2007 <sup>59</sup>	100	BIAspart 30/70	16	10.4	-2.8	42	R
53								
54	Robbins, 2007 <sup>30</sup>	157	Lispro 50/50	24	7.8	-0.7	56	R
55	Nauck, 2007 <sup>60</sup>	248	BIAspart 30/70	52	8.6	-0.9	24	R
56	Hirao, 2008 <sup>61</sup>	56	BIAspart 30/70	24	10.6	-3.0	32	R
57								
58	Rosenstock, 2008 <sup>62</sup>	187	Lispro 50/50	24	8.8	-1.85	54	R
59	Yang, 2008 <sup>63</sup>	160	BIAspart 30/70	24	9.5	-2.5	51	R
60	Yang, 2008 <sup>63</sup>	161	BIAspart 30/70	24	9.5	-2.82	66	R

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4	Liebl, 2009 <sup>64</sup>	178	BIAspart 30/70	16	8.4	-1.23	50	R
5	Raskin, 2009 <sup>65</sup>	102	BIAspart 30/70	34	8.1	-1.6	76	R
6	Buse, 2009 <sup>35</sup>	1045	Lispro 25/75	24	9.1	-1.9	47.5	R
7								
8	Cucinotta, 2009 <sup>66</sup>	200	BIAspart 30/70	36	8.9	-1.6	31	R
9								
10	Cucinotta, 2009 <sup>66</sup>	201	BIAspart 50/50	36	8.9	-1.9	51	R
11	Cucinotta, 2009 <sup>66</sup>	198	BIAspart 70/30	36	8.7	-1.5	38	R
12	Oyer, 2009 <sup>67</sup>	1625	BIAspart 30/70	24	9.9	-2.4	40	R
13								
14	Oyer, 2009 <sup>67</sup>	1624	BIAspart 30/70	24	9.9	-2.4	42	R
15	Oyer, 2009 <sup>67</sup>	1626	BIAspart 30/70	24	9.9	-2.5	42	R
16								
17	Strojek, 2009 <sup>41</sup>	225	BIAspart 30/70	24	8.5	-1.4	45	R
18								
19	Rosenstock, 2010 <sup>68</sup>	237	BIAspart 30/70	52	8.7	-0.8	27	R
20	Kalra, 2010 <sup>44</sup>	76	BIAspart 30/70	26	8.47	-1.22	40	R
21	Jain, 2010 <sup>69</sup>	242	Lispro 50/50	36	9.5	-1.76	35	R
22								
23	Roach, 1999 <sup>70</sup>	89	Lispro 25/75	26	9.2	-1.4	24	C
24	Herz, 2002 <sup>71</sup>	72	Lispro 25/75	16	9.8	-1.16	7.5	C
25								
26	Roach, 2003 <sup>72</sup>	57	Lispro50 + Lispro25	16	9.04	-0.9	15.5	C
27	Roach, 2003 <sup>72</sup>	59	Lispro 25/75	16	9.14	-1.0	15.5	C
28								
29	Tirgoviste, 2003 <sup>73</sup>	85	Lispro 25/75	16	9.45	-1.35	10	C
30	Christiansen, 2003 <sup>74</sup>	201	BIAspart 30/70	16	8.8	-0.6	16	C
31								
32	Kilo, 2003 <sup>75</sup>	46	BIAspart 30/70	12	9.5	-1.3	14	C
33	Scherthner, 2004 <sup>76</sup>	40	Lispro 50/50	12	8.4	-0.8	31	C
34	Niskanen, 2004 <sup>77</sup>	133	Lispro 25/75	12	8.5	-0.5	19	C
35	Niskanen, 2004 <sup>77</sup>	133	BIAspart 30/70	12	8.5	-0.35	15	C
36								
37	Boehm, 2004 <sup>78</sup>	58	BIAspart 30/70	24	9.45	-1.1	11.5	C
38								
39	Abrahamian, 2005 <sup>79</sup>	89	BIAspart 30/70	24	9.8	-2.2	31	C
40								
41	Raz, 2005 <sup>80</sup>	97	BIAspart 30/70	18	9.5	-0.5	5	C
42	Raz, 2005 <sup>80</sup>	93	BIAspart 30/70	18	9.6	-1.2	11	C
43	Ligthelm, 2006 <sup>81</sup>	196	BIAspart 30, 50, 70	16	9.1	-1.3	24	C
44	Kvapil, 2006 <sup>82</sup>	107	BIAspart 30/70	16	9.6	-1.6	19	C
45	Kvapil, 2006 <sup>82</sup>	108	BIAspart 30/70	16	9.3	-1.7	31	C
46								
47	Milicevic, 2009 <sup>83</sup>	68	Lispro 50+Lispro 25	24	9.7	-1.3	10.5	C
48								
49	Lund, 2009 <sup>84</sup>	52	BIAspart 30/70	52	8.15	-1.45	65.5	C
50	Lund, 2009 <sup>84</sup>	49	BIAspart 30/70	52	8.07	-1.17	58.5	C
51								
52								
53								
54	<b>Prandial Insulin: 12 RCTs, 13 arms</b>							
55	Bastyr, 2000 <sup>85</sup>	41	Lispro	12	10.0	-2.3	23	R
56	Kazda, 2006 <sup>23</sup>	52	Lispro	16	8.2	-1.2	40	R
57								
58	Holman, 2007 <sup>29</sup>	239	Aspart	52	8.6	-1.4	49	R
59	Bretzel, 2008 <sup>33</sup>	208	Lispro	48	8.7	-1.9	69	R
60	Hirao, 2008 <sup>61</sup>	61	Lispro	24	10.6	-2.8	33	R

1								
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4	Raz, 2009 <sup>36</sup>	557	Lispro	134	8.4	-0.7	28	R
5	Kawamori, 2009 <sup>86</sup>	127	Glulisine	16	9.0	-2.25	23	R
6	Kawamori, 2009 <sup>86</sup>	130	Glulisine	16	9.0	-2.07	52	R
7								
8	Gross, 2009 <sup>87</sup>	190	Lispro	24	8.2	-0.9	34	R
9	Anderson, 1997 <sup>88</sup>	772	Lispro	26	8,7	-0.5	14	C
10								
11	Ross, 2001 <sup>89</sup>	70	Lispro	24	10,3	-2.3	19	C
12	Forst, 2003 <sup>90</sup>	75	Lispro	26	7,5	-0.3	46	C
13								
14	Bretzel, 2004 <sup>91</sup>	75	Aspart	12	7,82	-0.9	58	C
15								
16								
17	<b>Basal-bolus insulin: 12 RCTs, 16 arms</b>							
18	Hollander, 2008 <sup>92</sup>	84	Glargine + Aspart	52	8.6	-1.4	36	R
19	Hollander, 2008 <sup>92</sup>	173	Detemir + Aspart	52	8.8	-1.8	37	R
20								
21	Rosenstock, 2008 <sup>62</sup>	187	Glargine + Lispro	24	8.9	-2.1	69	R
22	Bergental, 2008 <sup>93</sup>	136	Glargine + Glulisine	24	8.1	-1.4	73	R
23								
24	Bergental, 2008 <sup>93</sup>	137	Glargine + Glulisine	24	8.03	-1.5	69	R
25	Lankisch, 2008 <sup>94</sup>	162	Glargine + Glulisine	24	7.4	-0.4	36.5	R
26								
27	Lankisch, 2008 <sup>94</sup>	154	Glargine + Glulisine	24	7.3	-0.36	52	R
28	Liebl, 2009 <sup>64</sup>	537	Detemir + Aspart	16	8.5	-1.56	60	R
29								
30	Riddle, 2009 <sup>95</sup>	56	Glarg/Detem + any	24	8.3	-1.3	61	R
31	Raskin, 2009 <sup>96</sup>	251	Detemir + Aspart	24	8.4	-1.1	39	R
32								
33	Raskin, 2009 <sup>96</sup>	128	Glargine + Aspart	24	8.4	-1.4	54	R
34	Fritsche, 2009 <sup>97</sup>	153	Glargine + Glulisine	52	8.6	-1.3	47	R
35	Jain, 2010 <sup>69</sup>	242	Glargine + Lispro	36	9.3	-1.93	39	R
36								
37	Raslova 2004 <sup>98</sup>	195	Detemir + Aspart	22	8,11	-0.65	36	C
38	Haak, 2005 <sup>99</sup>	341	Detemir + Aspart	26	7,9	-0.3	31	C
39								
40	Yokohama, 2006 <sup>100</sup>	31	Glargine + Lispro	14	7,2	-0.6	70	C

HbA1c target <7%: R=reported; C=calculated

Table 2. Weighted R<sup>2</sup> for the overall population and subanalyses

Analysis	Arms (n)	Population	HbA1c Basal Median*	$\Delta$ HbA1c (%) Median*	HbA1c <7% Pooled (%)§ (95%, CI)	Weighted R <sup>2</sup>	
						Basal (independent) $\Delta$ HbA1c (dependent)	Basal (independent) Target (dependent)
Overall	135	38803	8.7 (8.4;9.1)	-1.4 (-1.7;-0.97)	40 (30;50)	0.485 (P < 0.001)	0.146 (P < 0.001)
Basal insulin	57	21615	8.7 (8.5;8.9)	-1.32 (-1.6;-0.9)	37 (27;50)	0.178 (P < 0.001)	0.195 (P < 0.001)
Biphasic insulin	49	11624	9.1 (8.5;9.6)	-1.4 (-1.9;-1.1)	35 (29;42)	0.418 (P < 0.001)	0.076 (P = 0.037)
Prandial insulin	13	2597	8.7 (8.2;9.2)	-1.4 (-2.2;-0.8)	37.5 (28;48)	0.717 (P < 0.001)	0.127 (P = 0.126)
Basal-bolus insulin	16	2967	8.35 (7.96;8.6)	-1.35 (-1.5;-0.6)	51 (41;61)	0.719 (P < 0.001)	0.000 (P = 0.526)

\*Median (interquartile range)

§Mixed effect model: estimates adjusted for the correlation within studies and heterogeneity between studies; CI = confidence interval

$\Delta$ HbA1c = decrement of HbA1c after intervention