

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



LSHTM Research Online

Anyanwagu, U; Mamza, J; Gordon, J; Donnelly, R; Idris, I; (2017) Premixed vs basal-bolus insulin regimen in Type 2 diabetes: comparison of clinical outcomes from randomized controlled trials and real-world data. Diabetic medicine. ISSN 0742-3071 DOI: <https://doi.org/10.1111/dme.13518>

Downloaded from: <http://researchonline.lshtm.ac.uk/4645845/>

DOI: <https://doi.org/10.1111/dme.13518>

**Usage Guidelines:**

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

**Premixed vs Basal-bolus Insulin regimen in Type 2 Diabetes: Comparison of clinical outcomes from randomised controlled trials and real world data.**

**U Anyanwagu, J Mamza, J Gordon, R Donnelly, I Idris**

Division of Medical Sciences & Graduate Entry Medicine,  
School of Medicine, University of Nottingham, United Kingdom

## **Novelty Statement**

Although evidence from RCT suggest that basal bolus insulin regimen is an effective insulin regimen, their effectiveness in real-world practice remains unclarified.

This study is the first to evaluate the concordance between data derived from RCT and real world estimates of HbA1c and weight between basal bolus compared with a premixed insulin regimen and assess their interrelationship between patient and relevant clinical characteristics, as determinants of concordance.

This study highlight specific discrepancies in the HbA1c reduction and weight change between real world outcomes versus RCT results. Greater baseline weight was associated with more favourable effect on weight outcome following premixed than basal bolus insulin regimen.

## Abstract

**Aim:** We evaluated the concordance between data derived from randomised controlled trials (RCT) and real-world estimates of HbA1c and weight change after 24 weeks of initiation of a basal-bolus compared with a premixed insulin regimen.

**Methods:** Data were pooled from 8 RCTs after a systematic review examining BB (n = 1893) or PM (n = 1517) regimens. RW data were extracted from the UK primary care dataset for BB (n = 7,483) or PM (n=10,744). t-tests were used to compute the mean differences between HbA1c and weight from baseline, ANOVA was used to compare between the populations. Linear regression analyses were used to determine the predictors of this change

**Results:** Both insulin regimens were associated with HbA1c reduction (-0.28% [real-world] and -1.4% [RCTs]) and weight gain (+0.27 kg [real-world]; +2.96kg [RCT]) but there were no significant differences between basal-bolus and premix. Discordances in the pattern of treatment response were, however, observed between real-world and RCT data for both insulin regimens. For any given baseline HbA1c, the change ( $\delta$ ) HbA1c in RCT was greater than in RW conditions and at any baseline weight above ~60kg, RCT population showed overall weight gain in contrast to slight weight loss in the RW population. Lastly, for both populations, while greater baseline weight was associated with reduced response to treatment, the association was much steeper for the RCT compared with real-world population. Also, greater baseline weight was associated with more favourable effect on weight outcome following premixed and to a lesser extent with basal bolus insulin regimen.

**Conclusion:** These results highlight discrepancies between real-world outcomes versus RCT results with respect to starting BB, (which is lower in real-world) or PM insulin regimens in people with Type 2 Diabetes.

## Introduction

Insulin therapy is essential for people with Type 2 diabetes (T2D), when diet and other glucose lowering therapy options have failed to achieve optimal HbA1c targets [1], to reduce the risks of long-term vascular complications [2,3]. Although the basal bolus and the premixed insulin are the two most widely used insulin regimens in T2D, there is no overall consensus regarding the most effective or optimal insulin regimen for people with T2D [4,5]. The basal-bolus regimen, which consists of multiple daily injections of rapid-acting insulin pre-prandially, in addition to a long-acting basal insulin, most closely mimics the pattern of insulin secretion [6], but the flexibility of this regimen is undermined by its complexity to count daily carbohydrate intake and adjust the insulin dose accordingly [7-9]. The premixed insulin regimen consists of a fixed ratio of rapid-acting insulin and intermediate insulin combined; thereby eliminating the need for patients to mix or adjust the insulin, themselves whilst also reducing the number of required daily injections. Although patients may find it easier to adhere to the premixed regimen [10] regular meal times and consistency in daily routine are sometimes necessary in order to gain maximum benefit and avoid the associated risk of hypoglycaemia.

Evidence from RCTs and meta-analyses have shown heterogeneous outcomes between basal-bolus and premixed insulin regimens [11-13]. As such, the choice of the optimal insulin regimen continues to be debated [14]. Although RCTs meet regulatory and scientific standards, they do not necessarily reflect what happens in real world [15]. As such, the use of trial derived estimates of clinical outcomes when used to underpin guidelines, may present a biased view of the relative outcomes of treatments when used in routine practice. Failing to account for this discrepancy may lead to suboptimal patients' outcomes and wasted healthcare resources.

We therefore aim to evaluate the concordance between data derived from RCT, real world estimates of HbA1c, and weight reduction after 24 weeks of initiation of basal bolus compared with a premixed insulin regimen and assess their interrelationship between clinical characteristics and relevant clinical profiles as determinants of concordance.

## **Methods**

### **Study Design and Data Sources**

Data were extracted from two sources- observational data from the UK primary care via The Health Improvement Network (THIN) and RCTs in people with T2D.

The search strategy and terms used in the systematic selection of these trials have been fully described in our previous study [16]. However, we added an additional exclusion criterion in which trials lasting less than 6 months were excluded. These selected eight RCTs [11, 12, 17-22] were randomised, double-blind parallel or crossover designs in which basal-bolus insulin regimen was compared to premix.

In the observational population, we pooled data from the THIN database on people with T2D who initiated insulin therapy (either basal-bolus or premix). THIN is the UK computerised anonymised longitudinal primary care records with details of over 10.5 million patients derived from 532 general practices within the UK, shown to be demographically representative of the dynamics of the UK population [23]. We have previously published diabetes-related outcomes in routine clinical practice using this database. [24,25]

### **Exposures and Outcomes:**

In both populations, the main exposure was insulin regimen- basal-bolus vs premix. The premix (biphasic) regimen intervention was defined as two or more injections of any brand of premixed insulin per day while the basal-bolus regimen was defined as any basal injection with at least a single bolus injection per day. These were specified in details in the treatment protocols of the RCTs, while in the observational data, these prescriptions were identified by their appropriate READ codes in the THIN database. The main outcomes were mean differences in glycaemic control (measured by HbA1c) and weight between the two population groups measured at 6 months and above.

### **Covariates:**

For both populations (RCTs and Observational), data on baseline demographics and patients' characteristics were obtained. Also, baseline and 6-month measurements of HbA1c and body

weight were obtained. Other important clinical measures as comorbidity states, medication use and other biochemical variables were obtained in the observational study population.

### **Statistical Analyses**

For both the RCTs and observational data, the difference between HbA1c at baseline and at 6 months (glycaemic control) was computed. Also, the difference in weight at baseline and 6 months will be computed. Generally, descriptive statistics was used to summarise the baseline variables in both population groups. Missing data among the baseline covariates in the real-world data were accounted for with multiple imputations using the chained equation model. Student t-test was used to determine the mean differences in HbA1c and weight between the insulin regimens at baseline and post 24 weeks. Linear regression analyses were conducted to identify the strongest predictors of glycaemic control and weigh change. Finally, we used ANOVA to compare the changes in HbA1c and weight between the insulin regimens and the study populations. Finally, we used ANOVA to compare the changes in HbA1c and weight between the insulin regimens and the study populations.

All analyses were conducted using Stata Software, version 14 with statistical significance put at a p-level  $\leq 0.05$ .

## **Results**

### **Baseline Characteristics**

In all populations, there were 21,637 participants with 3,410 in the RCT and 18,227 in the real world population. Among this, 9,376 received basal-bolus regimen, while 12,261 were on the premixed regimen.

In the observational (THIN) database population group, the overall mean age was 61.5 (SD13.8) years with the mean baseline HbA1c [72mmol/mol (8.7%) vs 72mmol/mol (8.7%)] and weight (90.7kg vs 92.1kg) in the premixed and basal-bolus groups respectively. Other important baseline variables in this group are summarised in Table 1. Weight, age, diastolic BP and comorbidity status differed significantly between both regimens at baseline. In the RCT population [9, 10, 15 -20], the mean HbA1c and weight were [74mmol/mol (8.9%) vs 74mmol/mol (8.9%)] and (85.6kg vs 85.6kg) in the basal-bolus and premixed insulin regimens respectively. Other important baseline variables are summarised in Table 2.

### **Change in HbA1c**

In the THIN database, there was a significant reduction from the baseline HbA1c of 70mmol/mol (8.6%) to 67mmol/mol (8.3%) (mean diff = 0.28%; 95%CI: -0.30, - 0.27;  $p < 0.0001$ ) after 6 months. Both the premixed and basal-bolus insulin regimens showed similar reduction at 6 months. There was better glycaemic control in the basal-bolus arm at 6 months of insulin initiation (mean diff = -0.08%; 95%CI: -0.11, -0.04;  $p = 0.0001$ )(Figure 1A).

Similarly, the RCT population reported a significant improvement in glycaemic control, with a mean reduction in HbA1c of 1.4% (95% CI: -1.87,-0.92;  $p < 0.0001$ ) at 6 months from baseline. There was a significant reduction in HbA1c at 6 months 74mmol/mol (8.9%) vs 58mmol/mol (7.5%); mean diff: 1.34%; 95%CI: -2.09, -0.6;  $p = 0.003$ ) in the premixed group; as was in the basal-bolus regimen 74mmol/mol (8.9%) vs 57mmol/mol (7.4%); mean diff: 1.44%; 95%CI: -2.20,-0.69;  $p = 0.0023$ ). No significant difference in glycaemic control was observed between the two insulin regimens after adjustment for age and baseline weight.

### **Change in Weight (Kg):**



Overall, there was a significant increase in weight after 6 months in the THIN population (mean diff: 0.27; 95%CI: 0.18, 0.35;  $p < 0.0001$ ), this represented an increase of 0.31kg (95%CI: 0.20, 0.42;  $p < 0.0001$ ) in the premix arm vs 0.21kg (95%CI: 0.07, 0.34;  $p = 0.002$ ) in the basal-bolus arm. Nonetheless, no significant difference in weight gain was recorded between these two (premixed vs basal-bolus) regimens at 6 months (Figure 1B).

The RCT population recorded a significant increase in weight from 88.9kg at baseline to 91.9kg at 6 months (mean diff = 2.96kg; 95%CI: 2.05 – 3.88;  $p < 0.0001$ ). In the premixed group, there was an increase in weight from 88.9kg to 91.2kg (mean diff: 2.26kg; 95%CI: 0.80, 3.71;  $p = 0.009$ ) while the basal-bolus group had a greater increase of 88.8kg to 92.6kg (mean diff: 3.67; 95%CI: 2.43 – 4.92;  $p = 0.0004$ ). In spite of these, there was no significant difference between the changes recorded between the insulin regimens - premixed (2.26kg) vs basal-bolus (3.67kg) at 6 months.

### **Predictors of response at baseline**

In the THIN data population, there was a weak correlation between baseline HbA1c and response to treatment ( $\delta$  HbA1c) because 20% of the variability in the change in HbA1c in this group was attributable to the HbA1c at baseline ( $r^2 = 0.20$ ; slope =  $-0.30$ ; 95% CI  $-0.31, -0.2$ ;  $p < 0.0001$ ). There was a very little correlation due to age (slope =  $-0.004$ ;  $p < 0.001$ ), gender (slope =  $-0.05$ ;  $p = 0.019$ ), and duration of diabetes (slope =  $-0.003$ ;  $p = 0.031$ ). In contrast, in the RCT population, there was a strong correlation between baseline HbA1c and  $\delta$  HbA1c. 88% of this variability in  $\delta$  HbA1c was attributable to the HbA1c at baseline ( $r^2 = 0.88$ ; slope =  $-1.43$ ; 95% CI  $-1.77, -1.08$ ;  $p < 0.0001$ ). There was a non-significant correlation with age (slope =  $0.04$ ;  $p = 0.941$ ) and weight (slope =  $-0.02$ ;  $p = 0.069$ ).

### ***HbA1c reduction as a function of Baseline HbA1c in premixed and basal bolus regimen***

In Figure 2, comparison is made between these two insulin regimens in real-world and RCT conditions. These showed similar patterns of response to treatment as a function of baseline HbA1c i.e. greater response to treatment with higher baseline HbA1c values but steeper in the RCT population in for both regimens. At baseline HbA1c values of 64mmol/mol (8.0%) and

62mmol/mol (7.8%), both populations showed no change in HbA1c at 6 months, but below these, both populations reported an increase in HbA1c value at 6 months, this being greater too in the RCT population. This same pattern was observed for basal-bolus. Thus for any given baseline HbA1c for both insulin regimens, the  $\delta$  HbA1c in RCT was greater than in real world conditions. No interaction with study populations was observed (RCT vs THIN, coefficient = 0.003,  $p = 0.965$ ).

#### Weight change as a function of Baseline Weight in premixed and basal bolus regimen

For changes in weight according to baseline weight, different response patterns were observed between different insulin regimens (Figure 3) in the RCT population. In the real-world population, there was a weak correlation between baseline weight and weight after 6 months. 2% of the variability in weight change was attributable to the weight at baseline ( $r^2 = 0.02$ ; slope =  $-0.049$ ; 95% CI  $-0.05, -0.04$ ;  $p < 0.0001$ ). This was independent of gender, age and duration of diabetes. In the RCT population, there was a slightly higher non-significant correlation between baseline weight and weight-change at 6 month as it shows that 49% the variability in weight change was attributable to the weight at baseline ( $r^2 = 0.49$ ; slope =  $0.06$ ; 95% CI  $-0.04, 0.15$ ;  $p=0.204$ ), independent of age (slope =  $0.07$ ;  $p = 0.74$ ).

The premixed group showed a slight negative correlation in real-world ( $r^2=0.03$ ; slope =  $-0.05$ ; 95% CI  $-0.06, -0.04$ ;  $p < 0.0001$ ), i.e. those with a baseline weight of more than 100kg experienced weight reduction, while those below 100kg at baseline, experienced weight-gain at 6 months (Figure 2a) but in the RCT population, this association was almost unity, ( $r^2 = 0.0005$ ; slope =  $-0.003$ ; 95% CI  $-0.17, 0.16$ ;  $p = 0.962$ ) – meaning that there was no change in weight at 6 months irrespective of baseline weight. For the basal-bolus treatment group, real world population showed a weak negative correlation ( $r^2 = 0.02$ ; slope =  $-0.05$ ; 95% CI  $-0.05, -0.04$ ;  $p < 0.0001$ ): slight weight reduction as baseline weight increases. Conversely, the RCT group showed a positive correlation ( $r^2 = 0.45$ ; slope =  $0.09$ ; 95% CI  $-0.02, -0.19$ ;  $p = 0.098$ ), i.e. more weight-gain at 6 months as baseline weight increases. Taken together, at any baseline weight above 60kg, while the RCT group showed a weight gain, the real-world group observed a slight reduction in weight.

#### HbA1c change as a function of Baseline Weight in premixed and basal bolus regimen

The change in HbA1c as a function of baseline weight for premixed and basal bolus insulin regimens, showed that for both real world and RCT populations, greater baseline weight was

associated with reduced response to treatment. However, the association was much steeper for the RCT compared with real world population. Furthermore, for the premixed population, for any baseline weight, response to treatment was greater in the RCT population compared with real world conditions up until weight of approximately 110kg, above which, response to treatment was greater for real world populations. Similarly, for the basal bolus insulin regimen, for any baseline weight, response to treatment was greater in the RCT population compared with real world conditions up until weight of approximately 110kg, above which, response to treatment was greater for real world populations up until 140kg weight, above which, response to treatment was slightly greater for real world populations

## **Discussion:**

This analysis compared the relative HbA1c and weight outcomes of premixed insulin regimen or the basal bolus insulin regimen in people with type 2 diabetes in RCT vs in real-world conditions. Despite the significant difference in HbA1c found with basal-bolus in this study, its clinical relevance is unclear and no difference in HbA1c and weight was noted between insulin regimens for both real-world and RCT populations at 6months. Discordance in the pattern of treatment response was however observed between the populations for both insulin regimens. While the present analysis confirms the expected relationship between baseline HbA1c and HbA1c reduction with either a premixed or a basal-bolus insulin regimen, the strength of this relationship was considerably more apparent in the RCT population compared with real world conditions. We observed a negative association between weight-change at 6months and baseline weight among patients receiving a premixed insulin regimen in both real-world and RCT populations, i.e. as baseline weight increases, the weights in these populations at 6 months slightly reduced, and more marked in the real-world populations. However for patients receiving a basal-bolus insulin regimen, discordance in response was observed between real world and RCT populations, i.e. a negative association (reduction in weight at 6months as baseline weight increases) in real-world conditions but a positive association (increase in weight at 6months as baseline weight increases) in the RCT population. Lastly, for both premixed and basal bolus insulin regimen, the expected relationship between baseline weight and response to insulin treatment was mainly apparent under RCT conditions.

The cause of the discrepancies in the HbA1c and weight response with premixed insulin or a basal bolus insulin regimen in real world conditions compared with RCT is not clear. However, insulin regimen is associated with hypoglycaemia and weight gain[26, 27], with the latter often occurring only during the first months following insulin initiation; and an important difference between the premixed and the basal bolus insulin regimen is that the latter can be more demanding due to increased frequency of insulin injections and dose adjustments.

Thus, it is tempting to speculate that the any discrepancies between real world and RCT is borne out of fear of hypoglycaemia, especially in the basal-bolus insulin regimen [26], weight gain [27], reduced compliance with a basal bolus insulin regimen or patients' ambivalence to up-titrate insulin doses under real-world conditions due to lack of monitoring, patient-education, or lack of rigid guidelines or protocols for patients to follow [28]. Fear of hypoglycaemia in real-world for example may explain the less apparent association between

baseline HbA1c and response to treatment in real world conditions compared with RCT for both insulin regimens. Other likely possible explanations include the relatively younger age of the RCT population; and the higher rate of comorbidities and selection bias in the real-world population.

Our observations that greater baseline weight was associated with more favourable effect on weight outcome following premixed and to a lesser extent with basal bolus insulin regimen should provide important reassurance that in routine clinical practice, meaningful reduction in HbA1c can be achieved without significant detrimental effect on weight. This observation was supported by findings from two other studies [29, 30]. In one study involving 155,917 patients who were recently initiated in insulin, Paul and colleagues reported that obese patients gain significantly less weight with insulin and that progressive reduction in body weight gain was observed with progressive increases in baseline BMI above 30 kg/m<sup>2</sup>, thought to be due to the use of less intensive insulin therapy [29]. Another reported a significant inverse association of baseline BMI with weight gain in a cohort of 2,179 patients with about nine years of median diabetes duration [30].

Interestingly, the converse relationship between baseline weight and weight change was observed in our RCT cohort who received a basal bolus, but not the premixed insulin regimen. This implies an increase propensity to weight gain with basal bolus insulin regimen compared with premixed insulin in an RCT setting, supported by our findings from a systematic review and meta-analysis comparing basal bolus and the premixed insulin [31,32]. In addition, the 4-T study reported that mean weight gain was higher in the prandial group than in either the biphasic group or the basal group [31].

This analysis is subject to some limitations inherent to observational studies, including potential confounders such as compliance, indication bias, effects on ethnicity and differences in insulin regimens or titration protocols used across different areas in the UK. We attempted to minimize this by restricting the analysis only to patients who initiated a specific insulin regimen. Importantly, we do not have robust information on hypoglycaemic events that may limit the success of a given therapy, patient education programme, use and frequency of glucose self-monitoring, frequency of insulin dose adjustment and rules for self-adjustment of insulin dose or adjustment by feeling which have been shown to be important confounders.[8,31,33] With regards to the analysis of the RCT data, our previous meta-analysis

of this area showed substantial heterogeneity was found in the meta-analysis on HbA1c change. This may be attributed to a number of confounding factors such as: poor study quality, small treatment groups, short study duration and different study designs. Lastly, we pooled trials and real world data using regular and analogue insulin because previous meta-analysis suggests similar HbA1c outcomes between the two types [28]. Despite these limitations, it is important to note that the emphasis of our study is a pragmatic approach to decision-making for initiation of insulin among patients who require insulin soon after diagnosis of diabetes in ‘real world’ clinical practice based on variables that are available to clinicians and to compare this with outcomes derived from RCT. This is because clinical trials involve strict adherence to treatment based on randomization to a given insulin regimen while in real world, the choice of insulin regimen involves the patient and takes other clinical and metabolic concerns into consideration. Additionally, unlike in RCTs which has a tight time schedule, treatment in real world setting is not limited by time. This confers a superior advantage to the evidence from real-world-situation because people with diabetes need to deal with an insulin regimen not only for 6 to 12 months like in RCTs but for a long, often life-long time.

In summary this work showed that there is discordance in the pattern and magnitude of treatment response observed between real world and RCT populations between the two insulin regimens. The ‘blunting’ of the expected relationship between baseline HbA1c and the response to treatment with either a premixed or a basal bolus insulin regimens in real world and the reverse association between weight change and baseline weight among patients receiving the two insulin regimens between real world and RCT populations, emphasised the importance of patient-factors that would determine the potential success of one insulin regimen compared to another. Choice of insulin regimen should therefore be individualised according to patients’ personal, social and clinical characteristics.

## References

1. DeWitt DE, Hirsch IB. Outpatients insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003; **289**: 2254–2264.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Engl J Med* 1993; **329**: 977–986.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10–Year follow-up of intensive glucose control in type 2 diabetes. *NEngl J Med* 2008; **359**: 1577–1589.
4. Garber AJ. Methods to enhance delivery of prandial insulin and basal-prandial insulin. *Diabetes Obes Metab* 2013; **15**(Suppl 1):11–17.
5. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32**: 193–203.
6. Hamaty M. Insulin treatment for type 2 diabetes: when to start, which to use. *Cleve Clin J Med* 2011; **78**: 332–342.
7. Beluchin E, Baz L, Muller N, et al. Frequency of self-adjustment of insulin dose and metabolic control in Type 2 diabetes -is there an association? *Diabet Med* 2013; **30**(3): e91-4.
8. Kramer G, Kuniss N, Kloos C, et al. Principles of self-adjustment of insulin dose in people with diabetes type 2 and flexible insulin therapy. *Diabetes Res Clin Pract* 2016; **116**: 165-70.
9. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. *Diabetes Care* 2010; **33**: 240–245.
10. Turner HE, Matthews DR. The use of fixed-mixture insulins in clinical practice. *Eur J Clin Pharmacol* 2000; **56**: 19–25.
11. Bowering K, Reed VA, Felicio JS, Landry J, Ji L, Oliveira J. A study comparing insulin lispro mix 25 with glargine plus lispro therapy in patients with Type 2 diabetes who have inadequate glycaemic control on oral anti-hyperglycaemic medication: results of the PARADIGM study. *Diabet Med* 2012; **29**: e263–272.

12. Fritsche A, Larbig M, Owens D, Haring HU. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes-results of the GINGER study. *Diabetes Obes Metab* 2010; **12**: 115–123.
13. Kloos C, Samann A, Lehmann T, Braun A, Heckmann B, Muller UA. Flexible intensive versus conventional insulin therapy in insulin-naive adults with type 2 diabetes: an open-label, randomized, controlled, crossover clinical trial of metabolic control and patient preference. *Diabetes Care* 2007; **30**(12): 3031-2.
14. Idris I, Pillai A, Fernando DJ, Thomson G, Tate H. Responders to insulin therapy at 18 months in adults with newly diagnosed diabetes: which insulin regimen? *Diabet Med* 2013; **30**: e95–100.
15. Schwartz D, Lellouch J (2009) Explanatory and pragmatic attitudes in therapeutic trials. *J Clin Epidemiol* 62:499–505
16. Wang C, Mamza J, Idris I. Biphasic vs basal bolus insulin regimen in Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetic Medicine*. 2015 DOI:10.1111/dme. 12694.
17. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). *Diabetes Research and Clinical Practice* 2008; **79**(1): 171-6.
18. Jain SM, Mao X, Escalante-Pulido M, Vorokhobina N, Lopez I, Ilag LL. Prandial–basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: initiate and progressively advance insulin therapy in type 2 diabetes. *Diabetes, Obesity and Metabolism* 2010; **12**(11): 967-75.
19. Levin PA, Zhang Q, Mersey JH, et al. Glycemic Control with Insulin Glargine plus Insulin Glulisine versus Premixed Insulin Analogues in Real-World Practices: A Cost-Effectiveness Study With a Randomized Pragmatic Trial Design. *Clinical Therapeutics* 2011; **33**(7): 841-50.
20. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes, Obesity and Metabolism* 2009; **11**(1): 45-52.
21. Miser WF, Arakaki R, Jiang H, Scism-Bacon J, Anderson PW, Fahrback JL. Randomized, open-label, parallel-group evaluations of basal-bolus therapy versus insulin lispro premixed therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral anti-hyperglycemic drugs: A non-inferiority intensification sub-study of the DURABLE trial. 2010.



<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010399254> (accessed (Miser) Department of Family Medicine, The Ohio State University College of Medicine, Columbus, OH, United States 32).

22. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care* 2008; **31**: 20–25.
23. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care* 2011; **19**(4): 251-5.
24. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med*. 2012 Jul 9;172(13):1005-11.
25. Anyanwagu U, Mamza J, Mehta R, Donnelly R, Idris I. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. *BMJ Heart*. 2016 May 23.
26. Polonsky WH, Thompson S, Wei W, Riddle MC, Chaudhari S, Jackson J, Bruno AS. Greater fear of hypoglycaemia with premixed insulin than with basal-bolus insulin glargine and glulisine: patient-reported outcomes from a 60-week randomised study. *Diabetes Obes Metab*. 2014; **16**(11):1121-7.
27. Pontiroli AE, Miele L, Morabito A Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab* 2011;**13**:1008–1019pmid:21645195
28. Concert CM, Burke RE, Eusebio AM, Slavin EA, Shortridge-Baggett LM. The Effectiveness of Motivational Interviewing on Glycemic Control for Adults with Type 2 Diabetes Mellitus (DM2): A Systematic Review. *JBI Libr Syst Rev*. 2012;**10**(42 Suppl):1-17.
29. Paul SK, Shaw J, Montvida O, Klein K. Weight gain in insulin treated patients by BMI categories at treatment initiation: New evidence from real-world data in patients with type 2 diabetes. *Diabetes Obesity Metabolism*. 2016 Aug 9. doi: 10.1111/dom.12761.
30. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care*. 2014; **37**(8):2108-13. doi: 10.2337/dc13-3010. Epub 2014 May 13

31. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; **361**: 1736–1744.
32. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *The Cochrane Database of Systematic Reviews*, 2006: CD003287
33. Muller N, Lehmann T, Gerste B, et al. Increase in the incidence of severe hypoglycaemia in people with Type 2 diabetes in spite of new drugs: analysis based on health insurance data from Germany. *Diabet Med* 2017. Jun 6. doi: 10.1111/dme.13397. [Epub ahead of print]

## Legend for Tables and Figures:

Table 1 - Baseline Characteristics in real world (THIN Data) population

Table 2 - Summary of baseline characteristics of the Randomised Clinical Trials

Figure 1:

Figures 1a and 1b show the mean difference in HbA1c (%) and weight (kg) between premix and basal-bolus insulin regimens in the RCT and real-world populations after 6 months of insulin initiation.

Figure 2:

Figures 2a and 2b show graphs depicting glycaemic control (measured by change in HbA1c) as a function of baseline HbA1c in type 2 diabetes population on insulin therapy after 24 weeks and above. Comparison is made between the real world (THIN data) and the RCT populations in people on premix (A) and basal-bolus (B) insulin regimen. The interaction coefficient is, for (A) -0.30,  $p < 0.0001$ ; and (B)  $-1.43$ ,  $p < 0.0001$ .

Figure 3:

Figures 3a and 3b show graphs depicting change in weight as a function of baseline weight (kg) in type 2 diabetes population on insulin therapy after 24 weeks and above. Comparison is made between the real world (THIN data) and the RCT populations in people on premix (A) and basal-bolus (B) insulin regimen. The interaction coefficient is, for (A)  $-0.049$ ,  $p < 0.0001$ ; and (B)  $0.06$ ,  $p = 0.204$ .

**Table 1**

<b>Baseline variable</b>	<b>Premix Insulin (n = 10,744)</b>	<b>Basal-bolus (n = 7,483)</b>	<b>Total (n = 18,227)</b>	<b>p-value for differences</b>
<b>Demographics</b>				
Age (yrs), Mean (SD)	61.5 (12.7)	61.5 (14.9)	61.5 (13.8)	0.015
Gender, No. (%)				
Male	5717 (53.2)	3978 (53.2)	9,695 (53.2)	0.946
Female	5027 (46.8)	3505 (46.8)	8,532 (46.8)	
Townsend deprivation, No(%)				
Least deprived	2024 (19.8)	1563 (21.7)	3,587 (20.6)	<0.001
2nd quintile	1989 (19.4)	1508 (21.0)	3,497 (20.1)	
3rd quintile	2229 (21.8)	1501 (20.9)	3,730 (21.4)	
4th quintile	2258 (22.0)	1505 (20.9)	3,763 (21.6)	
Most deprived	1742 (17.0)	1117 (15.5)	2,859 (16.4)	
<b>Clinical Covariates, Mean (SD)</b>				
HbA1c (%)	8.7 (1.8)	8.7 (1.9)	8.6 (1.8)	0.903
BMI (kg/m <sup>2</sup> )	32.5 (6.8)	32.6 (6.9)	32.4 (6.9)	0.082
Weight (Kg)	90.7 (18.5)	92.1(19.1)	90.8 (18.7)	<0.0001
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	<0.0001
SBP (mmHg)	136.4 (23.0)	136.2 (23.2)	136.4 (24.3)	0.122
DBP (mmHg)	76.5 (10.7)	75.6 (10.9)	75.9 (10.9)	<0.0001
TC (mmol/l)	4.5 (1.3)	4.5 (1.3)	4.5 (1.3)	0.370
HDL (mmol/l)	1.2 (0.5)	1.2 (0.5)	1.2 (0.4)	0.002
LDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	2.4 (1.01)	0.084
Triglyceride (mmol/L)	2.1 (1.2)	2.0 (1.2)	2.0 (1.2)	0.188
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)	0.012
eGFR (mls/min/1.73m <sup>2</sup> )	62.3 (21.0)	63.8 (21.5)	62.8 (21.8)	<0.0001
ACR (mg/mol)	5.8 (8.4)	5.9 (8.6)	5.8 (8.5)	0.830
Diabetes duration (yrs)	3.9 (6.7)	4.8 (5.7)	4.3 (4.9)	<0.0001
<b>Smoking status, No. (%)</b>				
Non-smoker	5179 (48.2)	3682 (49.2)	8,809 (48.3)	0.011
Current smoker	1498 (13.9)	1127 (15.1)	2,625 (14.4)	
Ex-smoker	4067 (37.9)	2674 (35.7)	6,793 (37.3)	
<b>Alcohol status, No. (%)</b>				
Non-drinker	3667 (34.1)	2249 (30.1)	5,916 (32.5)	<0.001
Current drinker	5840 (54.4)	4403 (58.8)	10,243 (56.2)	
Ex-drinker	1237 (10.5)	831 (11.1)	2,068 (11.3)	
<b>BMI Categories, No. (%)</b>				
≤ 24.9kg/m <sup>2</sup>	1451 (13.5)	1004 (13.4)	2,455 (13.5)	0.588
25-29.9kg/m <sup>2</sup>	2587 (24.1)	1756 (23.5)	4,343 (23.8)	
≥ 30kg/m <sup>2</sup>	6706 (62.4)	4723 (63.1)	11,429 (62.7)	
<b>Other GLTs, No. (%)</b>				
Metformin	9045 (84.2)	6548 (87.5)	15,593 (85.6)	<0.001
Sulphonylurea	8004 (74.5)	5790 (77.4)	13,794 (75.7)	<0.001
Thiazolidinedione	3009 (28.0)	2745 (36.7)	5,754 (31.6)	<0.001
GLP-1ar	1034 (9.6)	909 (1.2)	1943 (10.7)	<0.001
SGLT2	50 (0.5)	35 (0.5)	85 (0.5)	0.982
Glinides	422 (3.9)	368 (4.9)	790 (4.3)	0.001
DPP4i	1137 (10.6)	1432 (19.1)	2569 (14.1)	<0.001
<b>Use of Medications, No. (%)</b>				
Aspirin	10,647 (99.1)	7430 (99.3)	18,077 (99.2)	0.527
Antihypertensive	9684 (92.6)	6252 (88.6)	15,936 (91.0)	<0.001
LLT	9588 (91.7)	6388 (90.5)	15,976 (91.2)	0.005
<b>Comorbidities, No. (%)<sup>c</sup></b>				
MI	472 (4.4)	227 (3.0)	699 (3.8)	<0.001
CHD	3665 (34.1)	1795 (24.0)	5,460 (30.0)	<0.001
PAD	1649 (15.4)	759 (10.1)	2,408 (13.2)	<0.001
Heart Failure	1689 (15.7)	768 (10.3)	2,457 (13.5)	<0.001

Hypoglycaemia	2256 (21.0)	929 (12.4)	3,185 (17.5)	<0.001
CVA	1766 (16.4)	972 (13.0)	2,738 (15.0)	<0.001

---

*Abbreviations:* MET (metformin); SU (sulphonylurea); GLP-1RA (Glucagon-like peptide 1 receptor analogues); INS (insulin); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation)

Diabetes duration is time from first diagnosis of diabetes to date of commencement of insulin

---

**Table 2**

Study	Baseline HbA1c mmol/mol[%]		HbA1c at $\geq 24$ wks mmol/mol[%]		Baseline Weight (kg)		Weight (kg) at $\geq 24$ wks		Age (yrs)		Diabetes duration (yrs)		Total number (N = 3410)	
	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix	Basal	Premix
<b>Bowering et al, 2012</b>	75 [9]	74 [8.9]	56 [7.3]	54 [7.1]	72.8	73.8	75.7	76.6	56.7	56.3	10	10.6	214	212
<b>Fritsche et al, 2010</b>	70 [8.6]	69 [8.5]	56 [7.3]	61[7.7]	87	84.3	90.6	86.5	60.9	60.2	12.8	12.5	153	153
<b>Hirao et al, 2008</b>	90 [10.4]	88 [10.2]	62 [7.8]	60 [7.6]	62.5	62.1	NR*	NR	58.5	57.9	12.2	9.5	80	80
<b>Jain et al, 2010</b>	78 [9.3]	80 [9.5]	58 [7.5]	60 [7.6]	78.8	78.2	82	81.3	58.9	59.9	12	11.4	242	242
<b>Levin et al, 2011</b>	78 [9.3]	79 [9.4]	53 [7.0]	55 [7.2]	102.6	103.5	108.9	106.6	55.9	56.4	13.1	12.9	106	91
<b>Liebl et al, 2009</b>	69 [8.5]	68 [8.4]	53 [7.0]	55 [7.2]	NR	NR	NR	NR	61.7	60.3	9.4	8.9	541	178
<b>Miser et al, 2010 (Arm A)</b>	64 [8.0]	64 [8.0]	65 [8.1]	64 [8.0]	89.3	90.1	92.2	91.5	55.9	58.2	9.3	8.9	199	200
<b>(Arm B)</b>	64 [8.0]	64 [8.0]	66 [8.2]	66 [8.2]	91.9	93.6	94.2	92.8	55.4	54.5	9.6	10	171	174
<b>Rosenstock et al, 2008</b>	74 [8.9]	73 [8.8]	51[6.8]	53 [7.0]	99.8	99.1	104.3	103.1	55.4	54	11.2	10.9	187	187
<b>Mean Total</b>	<b>74 [8.9]</b>	<b>74 [8.9]</b>	<b>57 [7.4]</b>	<b>58 [7.5]</b>	<b>85.6</b>	<b>85.6</b>	<b>92.6</b>	<b>91.2</b>	<b>57.7</b>	<b>57.5</b>	<b>11.1</b>	<b>10.6</b>	<b>1893</b>	<b>1517</b>

*NR = Not reported*

*N = total number of all trial participants in these trials*

*Diabetes duration is the duration of diabetes as at the commencement of the trial*