

Comparison of Cardiovascular and Metabolic Outcomes in people with Type 2 diabetes on Insulin versus Non-insulin Glucose-Lowering Therapies (GLTs): A Systematic Review and Meta-analysis of Clinical Trials.

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## 1. Abstract

**Objectives:** To compare the cardiovascular and metabolic outcomes of Insulin versus non-insulin glucose lowering therapy (GLT).

**Methods:** We included randomised control trials (RCTs) which randomised patients aged >18 years with Type 2 Diabetes (T2D) to insulin vs non-insulin GLT. We used risk ratios (RR), risk difference (RD) and odds ratios (OR) with 95% confidence interval (95%CI) to analyse the treatment effects of dichotomous outcomes and mean differences (with 95% CI) for continuous outcomes.

**Results:** We included 18 RCTs with 19,300 participants. There was no significant difference in the risk of all-cause mortality and CV events between the groups (RR= 1.01; 95%CI: 0.96 - 1.06; p = 0.69). In 16 trials, insulin showed greater efficacy in glycaemic control (mean diff= -0.20; 95%CI: -0.28 to -0.11) but the proportion achieving HbA1c level of either  $\leq 7.0\%$  or  $7.4\%$  (53 or 57mmol/mol) was similar in both (OR=1.55; 95%CI= 0.92 to 2.62). The non-insulin group had a significant reduction in weight (mean diff = -3.41; 95%CI: -4.50 to -2.32) and an increase in the proportion of adverse events (54.7% vs 45.3%, p= 0.044), but the insulin group showed an (RR= 1.90; 95%CI: 1.44 to 2.51) increased risk of hypoglycaemia.

**Conclusion:** There was no difference in the risk of all-cause mortality and adverse cardiovascular (CV) events between Insulin and non-insulin GLTs. Insulin was associated with superior reduction in HbA1c; least reduction in weight and higher risk of hypoglycaemia. Both showed similar proportion of patients achieving HbA1c target. Non-insulin GLTs were associated with a higher risk in reported adverse drug events.

## 2. Introduction:

For many patients with type 2 diabetes (T2D), treatment intensification using additional antihyperglycaemic agents is required in order to achieve optimal glycaemic control and prevent long-term vascular complications.[1, 2] A variety of antihyperglycaemic agents are available but questions regarding the long term safety and efficacy of some of these agents have been raised. In addition, recent focus by international regulatory agencies on the cardiovascular (CV) safety profile of commonly used antihyperglycaemic agents[3, 4] have led to debate about the most appropriate choice of therapy for treatment intensification.

Amidst this, exogenous insulin remains to be one of the most established glucose lowering therapies available[5-10] and its use in people with T2D has grown markedly over recent years. More recently however, the effectiveness and safety of insulin therapy has been a subject of intense discussion.[11-13] Moreover, recent large epidemiological studies have reported adverse ~~cardiovascular~~ CV outcome and increase mortality with insulin compared with non-insulin therapy.[13, 14] While the possible mechanism behind the observed the association between insulin and adverse cardiovascular and metabolic outcomes and mortality remains unclear, it is hypothesized that these may include, but not limited to, hypoglycaemia and weight gain. Although insulin therapy is associated with HbA1c lowering, weight gain and increased risk of hypoglycaemia, comparative analysis between insulin and non-insulin anti-diabetic therapy on these parameters are currently not available. A systematic review of RCT on the CV safety of insulin compared with non-insulin therapy has also not been reported. Thus, despite extensive experience of the use of insulin in routine clinical practice, we contend that the safety and efficacy of insulin has not been subjected to similar scrutiny in an adequately powered RCT setting, as is currently required for new antihyperglycaemic agents.[3]

We therefore aimed to compare the benefits and harms of Insulin versus non-insulin glucose lowering therapy (GLT) as reported in RCT involving patients with T2D.

### 3. Methods:

#### 3.1. Search Strategy:

We searched the following electronic databases from January, 2005 to December, 2014: The Cochrane Library, Ovid MEDLINE, EMBASE, and International Pharmaceutical Abstracts. We also scanned the reference lists of the included clinical trials for studies that met our inclusion criteria. The search terms used are in Figure 1 of the Appendix.

#### 3.2. Study selection:

Two authors (UA and JM) searched and screened the titles of all studies to assess their relevance to this study in line with the inclusion criteria. Clinical trials were included if they were randomised; involved only adult (18 years and above) patients with type 2 diabetes; compared insulin with any non-insulin GLT irrespective of baseline GLT (so far as the only difference between both groups is insulin); reported clinical outcomes as all-cause mortality, cardiovascular (CV) events (Myocardial infarction, stroke, heart failure, and CV mortality) and metabolic outcomes (e.g. glycaemic control, change in weight, and events of hypoglycaemia); had an intervention period of at least 24 weeks; and conducted within the past ten years (2005-2014). The last two decades have witnessed unprecedented advancement in diabetes care and management with the emergence of newer antidiabetic agents. So, the last decade was chosen to reflect current trends in diabetes care and provide recent evidence that will further guide diabetes management. We used only published trials and restricted the language to only English language.

Abstracts of the selected studies were then retrieved and reviewed thoroughly for inclusion in line with the inclusion criteria. The full text copies of the trials that met the inclusion criteria were then retrieved. Studies in persons with type 1 diabetes; without a clear protocol; with mixed age groups; no clear drug-combinations or short follow-up duration (<24 weeks) were excluded. A period of 24 weeks has been shown to be adequate to explore the effect of the treatment on the study outcomes.[15, 16]

The finally selected studies were imported into Endnote referencing software[17] where duplicates from the different databases were removed. The flow chart graphically explains the pathway to the selection of studies (Figure 1).

### **3.3. Data Extraction and Risk of bias assessment:**

Independently, two authors (UA and JM) extracted data from the 18 selected studies which met our inclusion criteria into a self-designed record form. These included basic study characteristics as number of participants, gender, patients' description, characteristics of the trials, follow-up and outcome measures.

Using the Cochrane Handbook for Systematic Reviews of Interventions tool,[18] the authors independently assessed the risk of bias and quality of each included trial according to the following domains: allocation sequence, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data, and selective outcome reporting and other sources of bias as funding of trials and drug quality. The trials were classified as low, high or unclear risk of bias.

The primary outcomes were

- i. All-cause mortality and
- ii. CV events (defined as CV mortality, non-fatal myocardial infarction (MI), non-fatal stroke and heart failure).

The secondary outcomes were

- i. Metabolic outcomes as glycaemic control (defined by the mean reduction in HbA1c and the proportion of patients attaining a target HbA1c level); and mean reduction in weight.
- ii. Episodes of hypoglycaemia and
- iii. The number of reported adverse drug events.

### **3.4. Statistical Analyses:**

The extracted data were entered into Microsoft excel document and exported into The Review Manager Software version 5.3 which we used for all statistical analyses. For continuous outcomes (changes in HbA1c and weight), we computed the mean differences between both treatment groups. In doing this, we entered the actual mean differences in our analyses where these were provided in the trials and where not available, we computed the mean differences from the mean values recorded in the included trials.

Q-test and  $I^2$  statistics were used to test for heterogeneity between the trials. A cut off of  $I^2 \geq 50\%$  was used to define heterogeneity. Where  $I^2 > 50\%$ , the random model was used and where there is no significant heterogeneity, the fixed model was used.[18]

We used Risk Ratios (RR) or Odds Ratios (OR) with 95% confidence interval (95%CI) as the summary statistics for dichotomous variables (All-cause mortality; CV-outcomes; proportion of participants attaining the target HbA1c levels; and risk of hypoglycaemia; and number of reported adverse events).These were derived from the number of events and the total number of participants in each treatment group. For continuous variables, weighted mean difference and 95% CI was used to summarise the data. Studies with missing data for any outcome were not included in the meta-analyses.

We performed subgroup analyses for the secondary outcomes of mean reduction in HbA1c and weight to assess if there are significant differences in the estimates ~~based on~~ according to the class of drugs in the non-insulin arm using a test of interaction. We tested for interaction according to risk of bias. Also, we used the funnel plot and Egger's test to detect the possibility of publication bias in the included trials in our meta-analysis.

All results were presented in tables, flow chart, forest plots, funnel plots, and bias tables.

The review protocol was registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>) with the registration number [CRD42015024559](#). The subgroup analysis for weight and addition of a secondary outcome of reported adverse events were not captured in our original protocol.

## **4. Results:**

### **4.1. Literature Search Results:**

From the electronic searches, we identified 2,445 papers from the databases (Figure 1). Following the exclusion of duplicate reports and review of the titles, 2,172 were dropped. After abstraction, 28 citations were selected and their full papers retrieved. Further 10 studies were removed because two had no clearly defined intervention and comparator groups, one was published in Danish; another involved people with both type 1 and 2 diabetes while one was amongst cystic fibrosis patients; two were single arm and/or non-randomised; another had more than two comparator arms; one study compared different types of insulin versus altering insulin doses; another measured quality of life (QOL) as its outcome.

Though the ORIGIN trial was not very clear on the specific drugs in its standard care arm,[19] this large trial which explore CV risks was included in our meta-analysis based on the consistency of the use of Insulin Glargine in its insulin arm and to a large extent, the high probability of not including insulin in its standard care arm. Similarly, though DIGAMI-2 trial[20] had three arms, it was chosen the insulin and non-insulin arms were clearly defined and outcomes compared between these two. Finally, 18 clinical trials[15, 16, 19-34] were selected for meta-analysis (Figure 1).

### **4.2. Baseline Characteristics:**

A total of 19,300 participants were involved in the selected 18 RCTs in which 9476 were randomised to insulin and 9351 to non-insulin GLT. Table 1 describes the baseline pre-trial characteristics of the trial participants. Majority (68.8%) of these trials compared insulin with GLP-1 (mostly exenatide), other comparators were DPP-4 inhibitors (12.5%), thiazolidinediones (12.5%) and metformin (6.2%). Insulin glargine was used in 12 (68.8%) trials while Insulin NPH, lispro and degludec were used in one trial each. Eight trials compared Insulin glargine and Exenatide.[21, 22, 24-27, 30, 31] The trial duration ranged from 24 weeks to 6.2 years. The mean age range of participants was 53.6 to 61.2 years. Also,

the mean baseline HbA1c range was 7.6 to 9.7%; BMI: 28.8 – 34.1kg/m<sup>2</sup>; and diabetes duration: 4.5 to 11.5 years (Table 1).

In Table 2, the specific details of the trials- the treatment arms and a few outcome measures of interest- were highlighted

#### **4.3. Bias Risk Assessment:**

All the trials showed high risk of performance and detection bias. This is because all the trials were open-label with no blinding of participants and assessors except only one trial which reported blinding of assessors[27]. Conversely, the risk of selection bias was low for all trials except one pilot study[29] in which no random sequence was generated nor allocation concealed. The risk of attrition, reporting and academic biases were low in all the included trials (Figure 2, Appendix).

#### **4.4. All-Cause Mortality and Cardiovascular (CV) Events:**

The primary outcomes of all-cause mortality and CV events were only reported by two trials involving a total of 13,317 participants in which 6738 were randomised to insulin and 6579 to the non-insulin arm (Figure 2). We found no significant heterogeneity between the studies for any of these outcomes ( $\chi^2 = 3.53$ ,  $p = 0.47$ ,  $I^2 = 0\%$ ). A total of 5,546 composite events were reported (2836 vs 2710). There was no significant difference in the risk of All-cause mortality and CV events between both treatment groups (RR= 1.01; 95%CI: 0.96 - 1.06;  $p = 0.69$ ).

##### **4.4.1. Risk of All-Cause Mortality:**

A total of 2,158 all-cause deaths occurred in the two included trials (1104 vs 1054). There was an equal risk of all-cause mortality between the two treatment arms (RR= 1.00; 95%CI: 0.93 - 1.08;  $p = 0.97$ ) (Figure 2).

##### **4.4.2. Risk of Cardiovascular Events:**

In Figure 2, our meta-analysis showed no significant difference in the risk of cardiovascular deaths in both treatment arms in the two trials which reported CV deaths ( $n = 1319$ ; RR= 1.02; 95%CI: 0.92 - 1.13;  $p = 0.65$ ). There was no heterogeneity among these studies ( $p = 0.69$ ). A total of 735 events of non-fatal myocardial infarction were reported with a risk ratio



of 1.07 (95%CI: 0.93 – 1.24;  $p = 0.32$ ). Similarly, no significant difference was observed in the risk of non-fatal stroke ( $n = 663$ ; RR= 1.04; 95%CI: 0.90 - 1.21;  $p = 0.56$ ) and heart failure ( $n = 671$ ; RR= 0.90; 95%CI: 0.77 - 1.04;  $p = 0.15$ ). We could not detect any evidence of publication bias in these trials in the meta-analysis for the risk of CV events. The funnel plot (Figure 3a, Appendix) and the Egger's test to detect any asymmetry in the funnel plot yielded no significant finding ( $p$ -value = 0.285).

#### **4.5. Glycaemic Control:**

##### **4.5.1. Mean Changes in HbA1c level:**

Only 16 of the 18 trials ( $N = 5201$ ) reported mean changes in HbA1c in both treatment groups. Of these, three trials[22, 25, 33] reported only the mean changes in each arm. So, we computed the mean difference between both treatment groups, using the mean difference of each arm. Overall, insulin showed greater efficacy in glycaemic control compared to non-insulin GLTs ( $n = 5201$ , mean difference= -0.20; 95%CI: -0.28 to -0.11; heterogeneity  $I^2 = 88\%$ ;  $p < 0.00001$ ) (figure 2). Tests of interaction showed no significant difference between the trials based on the risk of bias ( $p = 0.61$ ).

Figure 3 shows the comparison between insulin and different drug groups in the non-insulin arm. There was a significant heterogeneity between the subgroups.

Tests of interactions showed significant subgroup differences according to the drug groups in the non-insulin arm ( $I^2 = 84.3\%$ ;  $p = 0.0003$ ). With the GLP-1 analogues, 11 trials, involving 1,796 and 1,821 participants in the insulin and GLP-1 arms respectively, showed that insulin was associated greater glycaemic efficacy ( $n = 3,617$  mean difference= -0.13; 95%CI: -0.21 to -0.05; heterogeneity  $I^2 = 79\%$ ;  $p < 0.001$ ) compared to GLP-1 analogues. Only two trials with a total of 247 participants compared the Thiazolidinediones (127) with Insulin (120). The two trials showed no heterogeneity between them ( $p = 0.57$ ). Insulin showed greater glycaemic efficacy compared to the TZDs ( $n = 247$ , mean difference= -0.17; 95%CI: -0.30 to -0.05; heterogeneity  $I^2 = 0\%$ ;  $p < 0.007$ ). Two trials compared the DPP4 inhibitors with insulin. Compared to DPP4 inhibitors, insulin showed greater reduction in HbA1c ( $n = 452$ , mean difference= -0.52; 95%CI: -0.67 to -0.36; heterogeneity  $I^2 = 34\%$ ;  $p < 0.00001$ ). One trial

compared biguanides (metformin) to insulin and showed the superiority of insulin in glycaemic control (n=214, mean difference= -0.22; 95%CI: -0.39 to -0.05; p = 0.01).

#### **4.5.2. Proportion achieving a target HbA1c level:**

Ten trials with a total of 4,107 participants reported the proportion of patients achieving a target HbA1c level. In nine, the target was 7.0% (53mmol/mol) while one[25] had 7.4% (57mmol/mol) as its target. The included trials showed a significant heterogeneity ( $I^2 = 93\%$ ,  $p < 0.00001$ ) but showed no significant difference between insulin and non-insulin groups in achieving a glycaemic control level of  $\leq 7.5\%$  (n= 4107; OR= 1.55; 95%CI = 0.92 to 2.62; Heterogeneity  $I^2 = 93\%$ ;  $p=0.10$ ) (Figure 4, Appendix).

#### **4.6. Changes in Weight:**

A total of 16 trials with 17,795 participants reported mean changes in weight. One trial[29] reported mean change in BMI and was excluded in this meta-analysis. The non-insulin group had a significant reduction in weight from baseline to the endpoint than the insulin group (n= 17,795; mean diff = -3.41; 95%CI: -4.50 to -2.32; Heterogeneity  $I^2 = 100\%$ ;  $p < 0.00001$ ).

There was a significant interaction between the subgroups of the non-insulin ( $p < 0.00001$ ). We observed a significant mean weight reduction of 4.23kg in the GLP-1 analogues compared to insulin (n= 3704, mean diff = -4.23; 95%CI: -4.79 to -3.67; Heterogeneity  $I^2 = 90\%$ ;  $p < 0.00001$ ). In the only trial involving the TZDs, insulin showed a mean reduction of 1.4kg in weight compared to rosiglitazone (n= 217; mean diff: 1.40; 95% CI: 1.29 to -1.51;  $p < 0.00001$ ). On the contrary, the DPP4 inhibitors showed a significant reduction in weight (n=927; mean diff = -2.10; 95%CI: -3.31 to -0.89; Heterogeneity  $I^2 = 100\%$ ;  $p = 0.0007$ ) compared to insulin; while the metformin group showed a mean weight reduction of 0.1kg compared to a mean weight gain of 3kg by the inhaled insulin- Exubera (n= 410; mean diff = -3.14; 95%CI -3.71 to -2.57;  $p < 0.00001$ ). Finally, the standard care arm of the ORIGIN trial showed a mean weight reduction of 2.10kg compared to the insulin glargine arm (n= 12,537; mean diff: -2.10; 95%CI: -2.11 to -2.09;  $p < 0.00001$  as shown in Figure 4.

#### **4.7. Hypoglycaemia events:**

The pattern of reporting hypoglycaemia differed among the trials and this made it difficult for the reports of five trials to be included in the meta-analysis. Most trials defined it as an event characterised by simple symptoms as sweating, palpitations, hunger pangs and lethargy irrespective of confirmatory blood glucose less than 4.0mmol/L. For this meta-analysis, we defined severe hypoglycaemia as that which may necessitate assistance from another person; or associated with recovery after oral carbohydrate, glucagon or glucose administration; or with blood glucose less than 2.0mmol/L.

Figure 5 shows the proportion of adverse treatment effect represented by the events of hypoglycaemia as reported in 12 of the trials comprising 16,143 participants. There was almost a two-fold increased risk of hypoglycaemia in the participants on insulin therapy compared to those on non-insulin therapy (RR= 1.90; 95%CI: 1.44 to 2.51; Heterogeneity  $I^2 = 91\%$ ;  $p = 0.0001$ ).

#### **4.8. Reported adverse events:**

There were variations in the pattern, proportions, measures and number of adverse events reported in the different trials. These were either reported as the proportion of people with adverse drug-related events, and/or number of reported adverse events. One trial did not report any adverse event.[29] The overall proportion of reported adverse drug-related events was slightly higher in the non-insulin than in the insulin group (54.7% vs 45.3%,  $p = 0.044$ )

In the insulin group, the most reported adverse event was nasopharyngitis (21.08%) compared to nausea (42.71%) in the non-insulin group. Other common symptoms associated with insulin groups are headache (13.76%), diarrhoea (8.73%), influenza (6.0%), and cough (5.38%) while nasopharyngitis (17.93%), diarrhoea (16.69%), headache (14.72%), vomiting (12.9%) and gastrointestinal pain (7.87%) were most commonly reported in the non-insulin group (Table 3).

Only 12 trials with 2414 and 2363 participants in the non-insulin and insulin groups respectively reported the number of those with adverse drug-related events which we included in the meta-analysis (Figure 6). The non-insulin arm had 13 additional people per 100 with adverse drug-related, compared to the insulin arm (Risk diff = 0.13; 95%CI = 0.05 – 0.21; Heterogeneity  $I^2 = 91\%$ ;  $p = 0.002$ ). The fixed effect model showed no significant difference between both treatment groups ( $p = 0.236$ ).

## **5. Discussion:**

This meta-analysis involving 18 trials with 19,300 participants compared CV and metabolic outcomes between insulin and non-insulin GLTs in adult patients with type 2 diabetes. Data for meta-analysis for CV outcomes were provided by only 2 trials involving 13,317 participants and showed no difference in the risk of all-cause mortality; cardiovascular deaths, non-fatal MI, non-fatal stroke, heart failure and a composite of these events in the insulin vs non-insulin treatment groups. Insulin showed superior efficacy in glycaemic control; while the non-insulin treatment arm consistently showed a reduction in weight. The risk of hypoglycaemia increased almost 2-folds with insulin, while adverse events were slightly significantly higher in the non-insulin arm.

All the included trials lasted for more than 24 weeks, which in our view was sufficient to establish a biological plausibility between these GLTs and the outcomes of interest. All trials had a low-risk of bias and this helped to mitigate the risk of overestimation of benefits and underestimation of risks associated with trials with high risk of bias.[35]

The DIGAMI-2 trial population was drawn from patients with clinically diagnosed diabetes, and established CV risk. We pooled and compared data from only two arms (insulin vs non-insulin GLTs) of the three-arm trial.[20] In the ORIGIN trial,[19] the population comprised both established cases of diabetes; people with impaired fasting plasma glucose and impaired glucose tolerance. Both trials involved patients who were at very high risk of cardiovascular event. Similarly, all the data were used in our analysis with the standard care arm (defined as any GLT apart from insulin glargine, based on the investigators' best

judgement and prevailing local guidelines), used as the non-insulin arm of our analysis. Whilst this trial did not report any CV outcome specifically for people with established case of diabetes, we nonetheless used both in our meta-analysis. In addition, the ORIGIN trial's definition of CV deaths was that of exclusion. This implies that our finding should be interpreted with caution. The novel findings of the UKPDS study[36, 37] of the potential cardio-protective effect of insulin but this has not been consistent with other clinical trials and recent observational studies. So, the findings of our study seem to suggest that insulin may have similar cardiovascular effect, compared to other non-insulin GLTs.

Insulin showed better glycaemic control than non-insulin therapy but there was no statistically significant difference between both treatment groups in the proportion of participants achieving the target HbA1c levels ( $\leq 7.0$  or  $\leq 7.4\%$ ) ( $\leq 53$  or  $\leq 57$ mmol/mol). In a meta-analysis of 5 major trials comparing intensive and standard treatments, a reduction in HbA1c by 0.9% in the intensive arm resulted in 17% reduction in non-fatal MI and 15% reduction in coronary heart disease but no effect on stroke [38]. The UKPDS study showed a 21% reduction in any diabetes-related endpoint [39] and a meta-analysis showed an 18% increased risk of any CVD per unit rise in HbA1c level [40]. A retrospective observational study using UK primary care database however have shown a U-shaped association between HbA1c level and mortality among insulin users,[41] implying that intensive glycaemic control in itself may also portend the same adverse event that it tries to avert.

In the present study, we also observed that insulin was associated with 2.65kg weight gain compared to the non-insulin group. Insulin-associated weight gain has been described in many studies and this weight gain can be excessive, affecting cardiovascular risk factors.[42-45] Fourteen of our included trials showed that insulin was associated with increase in weight compared to its comparators while in contrast, a single-arm 14-week trial of the PREDICTIVE study, using insulin detemir, showed no weight gain in both types 1 and 2 diabetics[46]. This should be interpreted with caution due to the short trial duration, heterogeneity of the population studies and the different measures of outcomes among the participants. Weight gain has been shown to worsen all elements of CV risk profile—dyslipidaemia, hypertension, insulin-resistance and elevated fibrinogen—in a continuous graded fashion[47, 48]. In a vicious cycle, weight-gain associated insulin resistance increases

the demand for exogenous insulin which in turn leads to insulin-associated weight-gain which may further worsens cardiovascular risk and insulin resistance.

This study also showed that insulin is associated with 80% increased risk of hypoglycaemia than the non-insulin comparator group. This is consistent with those of major clinical trials as the ADVANCE, UKPDS, VADT and ACCORD which showed higher (19% up to 3-fold) risks of hypoglycaemia following intensive glycaemic control with insulin and other GLTs.[49-53] Hypoglycaemia is a well-known side effect of antihyperglycaemic agents and is associated with sympathetic surge and release of catecholamines with resulting tachycardia, raised BP and other haemodynamic changes which increased risk of an atherosclerotic event.[54] This link is best explained by resultant increased myocardial activity, platelet-aggregation and activity, and haematocrit which can trigger cardiac and ischaemic events in diabetic (high-risk) patients.[55-58] None of these studies however compared between insulin and sulfonylurea, the latter an important glucose lowering therapy which is known to be associated with an increased risk of hypoglycaemia.

We also reported that the risk of other severe and non-severe drug-related adverse events was greater in the non-insulin than insulin arms. This, however, had no significant effect on the rate of drop outs within the individual trials.

### 5.1. Strength and Limitations:

This systematic review and meta-analysis derives its strength mostly from the use of only RCTs, the number of trials (totalling 18) and the large number of participants (19,300) involved, which provided enough statistical power to detect any true effect.

One limitation of this study is inadequate blinding of participants and personnel, leading to the high risk of performance bias; and the non-blinding of assessors except in one trial[27] which led to a high risk of detection bias. As this limitation mirrors that of the included trials, these biases were mitigated by the fact that these outcomes (HbA1c and weight) were objectively assessed. Similarly, the non-standardised format of reporting the adverse events associated with the treatment groups could have led to either under- or over-reporting of events, as well as selective reporting. Other limitations include the variation in the study

design between the studies; the broad classification of different classes of GLTs into only two groups despite the variations in their mechanisms of action and effect on known CV risk factors; and the fact that our analysis was limited only to published literature. Finally, most studies failed to adequately explore the impact of some CV risk factors that might predict adverse CV events in the treatment groups.

## **6. Conclusion:**

Insulin showed similar risk of adverse CV outcomes with non-insulin GLTs but was associated with superior reduction in HbA1c. Also, we showed no difference in the proportion of patients achieving HbA1c target between both groups but observed that weight reduction was more in the non-insulin group. There was a 2-fold risk of hypoglycaemia with insulin but adverse events were more common in the non-insulin group. In view of CV outcomes, further studies with well-defined distinct treatment groups in a well-powered clinical trial are needed. This should be in line with the current requirement by international agencies that new antihyperglycaemic agents not only show glucose lowering ability, but also not associated with clinically meaningful increases in cardiovascular events.

These findings have implications for clinical practice. Therefore, individually-tailored holistic treatment strategy should be initiated, weighing the benefits of preventing microvascular complications and the risks of adverse cardiovascular and metabolic outcomes while incorporating lifestyle interventions.[59-61]

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## **Legend:**

Figure 1: Flow chart of study identification and selection

Figure 2: Forest Plot showing the risk of all-cause mortality and CV events between insulin and non-insulin treatment groups

Figure 3: Forest plot for the mean change in HbA1c (%) between insulin and non-insulin treatment groups, stratified by the different drug classes of the non-insulin group

Figure 4: Forest plot for the mean change in weight (Kg) between insulin and non-insulin treatment groups, stratified by the different drug classes of the non-insulin group

Figure 5: Forest Plot showing the risk of hypoglycaemia in insulin vs non-insulin treatment groups

Figure 6: Forest plot for the risk of adverse events between the insulin vs non-insulin treatment groups

## **Appendix**

Figure 1: Search Terms

Figure 2: Risk of bias summary showing authors' judgements about each risk of bias item for each included study.

Figure 3. Funnel plot showing Egger's asymmetry test for publication bias in the trials for the risk of CV events.

Figure 4: Forest Plot for the proportion attaining target HbA1c between the treatment groups.



**Table 1: Baseline Characteristics of Included Trials**

<b>Trial</b>	<b>No<sup>†</sup></b>	<b>Sex<sup>‡</sup> F(%)</b>	<b>Population</b>	<b>Trial drugs</b>	<b>Age (yrs)</b>	<b>Diabetes duration (yrs)</b>	<b>HbA1c (%)</b>	<b>Weight (Kg)</b>	<b>BMI (Kgm<sup>-2</sup>)</b>	<b>Trial duration</b>
<b>Aschner et al (2012)[15]</b>	515	49	Insulin-naïve T2D patients taking only metformin with HbA1c $\geq$ 7% and <11%	Insulin glargine vs Sitagliptin	53.6 (8.8)	4.5 (1.9-8.2)*	8.5(1.1)	83.8 (18.2)*	31.1(4.9)	24wks
<b>Barnett et al (2006)[16]</b>	427	47	T2D sulphonylurea (SU) failures with HbA1c 8-12%.	Insulin NPH vs Metformin	60.4 (35-79)*	9.2 (0.5-37.3)*	9.7 (1.1)	80.1 (50-136)*	28.8 (20-57)*	24wks
<b>Barnett et al (2007)[21]</b>	138	53	T2D aged $\geq$ 30yrs on Metformin (MET) $\pm$ SU failures with HbA1c $\geq$ 7% and <11%, BMI>25 and <40kgm <sup>-2</sup> and varying body weight	Insulin glargine vs Exenatide	54.9(0.8)	7.4(0.4)	9.0(0.1)	84.8(1.4)	31.1(0.4)	32wks
<b>Bunck et al (2009)[22]</b>	69	35	MET-treated T2D at a stable dose for 2 months and no other GLTs 3 months prior to screening.	Insulin glargine Vs Exenatide	58.4(1.4)	5.7(0.8)	7.6 $\pm$ 0.1	92.4(2.4)	30.1 (0.6)	52wks
<b>D'Alessio et al (2014)[23]</b>	798	46	T2D >1yr duration; HbA1c $\geq$ 7.5 and $\leq$ 12%; BMI: 25-40kgm <sup>-2</sup> ; on MET ( $\geq$ 1g/day) $\pm$ SU or Glinides or DPP-4i > 3 months	Insulin glargine vs Liraglutide	57(9)	9(6)	9.0(1.1)	90.5 (16.7)	31.9(4.2)	24wks
<b>Davies et al (2009)[25]</b>	235	32	T2D with BMI>27kgm <sup>-2</sup> and elevated cardiovascular risk, inadequately controlled on 2-3 oral GLTs.	Insulin glargine vs Exenatide	56.5(9.1)	8.7(4.5)	8.65(0.7)	99.5(18.3)	34.1(5.3)	26wks
<b>Davies et al (2013)[24]</b>	222	34	T2D adults not achieving adequate glycaemic control using MET or MET+SU	Insulin detemir vs Exenatide	58.5(10)	7.5(5.5)	8.36(0.9)	97.3(16.4)	33.7(4.7)	26wks
<b>de Wit et al (2014)[34]</b>	50	38	Insulin-users with T2D with weight gain $\geq$ 4% following $\leq$ 16months insulin therapy, HbA1c: $\geq$ 6.5 and <8%.	Insulin vs Liraglutide	58 (9)	8(6.1)	7.4(0.7)	100(19.3)	34 (7)	26wks
<b>Diamant et al (2010)[27]</b>	456	47	Adult T2D with suboptimum glycaemic control despite use of max tolerated dose of GLTs $\geq$ 3months	Insulin glargine vs Exenatide	58(9.5)	7.9(6)	8.3(1.1)	90.9(17.5)	32(5)	26wks



<b>Diamant et al (2012)[26]</b>	467	NR	Adult T2D who failed to maintain adequate glycaemic control with MET alone or MET+SU	Insulin glargine vs Exenatide	NR <sup>#</sup>	NR	8.3	NR	NR	84wks
<b>Diamant et al (2014)[28]</b>	510	52	T2D patients treated with insulin glargine and MET±SU, HbA1c: 7-19% and BMI: 25.0kgm <sup>-2</sup>	Insulin lispro vs Exenatide	59.5(9.5)	11.5 (8-17)*	8.3(1)	90.1(16.9)	32.5(4.7)	30wks
<b>DIGAMI-2 (2011)[20]</b>	1253	33	T2D patients with suspected acute myocardial infarction	Insulin (INS) vs INS +Non-INS GLTs	68.3(10.9)	8.14(8.4)	7.68(1.7)	NR	28.3(4.6)	2.1 years (with a median follow up of 4.1-8.1 years)
<b>Dorkhan et al (2009)[29]</b>	30	34	T2D patients with inadequate glycaemic control with MET+SU	Non-insulin GLTs vs Insulin glargine	61.2(7.7)	10.3(6.8)	8.2(1.5)	NR	31.2(5.8)	26wks
<b>Heine et al (2005)[30]</b>	549	44	T2D patients with inadequate glycaemic control (HbA1c: 7-10%) with MET+SU	Pioglitazone vs Insulin glargine	58.9(9.2)	9.6(5.9)	8.3 (1.0)	87.9(17.4)	31.4(4.5)	26wks
<b>Matyjaszek-Matuszek (2013)[31]</b>	80	56	T2D adults (30-70yrs), stable on optimal doses of MET+SU ≥3months, and BMI:25-45kgm <sup>2</sup>	Exenatide vs Insulin glargine	60(9.0)	8.4(5.14)	7.9(0.9)	85.7(16.7)	32.5(4.82)	26wks
<b>ORIGIN (2012)[19]</b>	12537	35	Outpatients with cardiovascular risk factors and T2D or IFG and IGT	Standard Care vs Insulin	63.6(7.8) 63.5(7.9)	5.5(6.1) 5.3(5.9)	6.4 (5.8-7.2)*	83.3(16.8) 83.1(17.3)	29.8(5.2) 29.9(5.3)	6.2 years
<b>Tsimikas et al (2013)[32]</b>	458	41	Insulin-naïve T2D (>6mths), HbA1c: 7-11%, BMI≤40kgm <sup>-2</sup> , treated with 1-2 non-insulin GLTs.	Insulin degludec vs Sitagliptin	56(10.8)	7.7(6.0)	8.9(1.0)	85(19.6)	30.4(5.2)	26wks
<b>Rosenstock et al (2006)[33]</b>	219	49	Insulin naïve, ≥18yrs T2D without CV risk factors, on MET and SU 3 months and above	Insulin glargine vs Rosiglitazone	55.6(11)	8.3(5.45)	8.8(1.0)	NR	34.(6.7)	24wks

*\*Median and Interquartile range. #NR= Not Reported. †Population at the beginning of the trial. ‡F= Females (Percentages approximated to the nearest whole number)  
DIGAMI-2: Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction, ORIGIN: Outcome Reduction with an Initial Glargine Intervention*

**Table 2: Trial Interventions and Outcome measures**

Trial	Design Type	Total <sup>a</sup>	Intervention groups	Baseline antidiabetics	Trial regime (dosage)		Outcome measures <sup>b</sup>
					Insulin	Comparator drug	
<b>Aschner et al (2012)[15]</b>	Randomised, Open-label, Parallel-arm, Controlled trial	515	Insulin glargine (250) Vs Sitagliptin (265)	Metformin	Subcutaneous dose of 0.2 unit/kg to attain fasting plasma glucose of 4.0-5.5mmol/L and increased or decreased by 2units respectively when below or above this range	Sitagliptin 100mg daily orally.	HbA1c Weight Hypoglycaemia at 6months
<b>Barnett et al (2006)[16]</b>	Randomised, open-label, parallel arm, Controlled trial Divided into two arms (HbA1c <9.5 and >9.5) before randomisation.	427	Insulin NPH(225) Vs Metformin(202)	Sulphonylurea	Inhalation (INH) in 1- and 3-mg dose blister packs	1g twice daily	Change in HbA1c
<b>Barnett et al (2007)[21]</b>	Randomised, Open-label, Crossover, Controlled trial	138	Insulin glargine (70) Vs Exenatide (68)	Metformin +/- Sulphonylurea	Once daily at bedtime targeting a fasting serum glucose level ≤5.6mmol/L for 16 weeks, then switch over to comparator after 16weeks	5µg BD for the first 4 weeks and 10µg thereafter. Then switch over to comparator after 16weeks	HbA1c, Weight FPG <sup>1</sup>
<b>Bunck et al (2009)[22]</b>	Randomised, Open-label, Parallel-arm, Controlled trial	69	Insulin glargine (33) Vs Exenatide (36)	Metformin	Initial dose of 10 IU to attain a glucose level of 4.5 and 5.5 mmol/L increased or decreased by 2 units when above or below this range respectively.	Initiated dose of 5 µg BD for 4 weeks followed by 10 µg BD, titrated to a max dose of 20 µg.	B-cell function, HbA1c, Body weight
<b>D'Alessio et al (2014)[23]</b>	Randomised, open-label, Parallel-arm, Controlled trial with a 24-wk extension phase with crossover	798	Insulin glargine (489) Vs Liraglutide (489)	Metformin +/- Sulphonylurea	Adjusted (titrated)every 3 days to target a fasting plasma glucose of 4.0-5.5mmol/L	0.6mg once daily increased to 1.2mg and 1.8mg daily weekly according to response.	HbA1c Weight Hypoglycaemia

<b>Davies et al (2009)[25]</b>	Randomised, Open-label Parallel-arm, Controlled trial	235	Insulin glargine (117) Vs Exenatide (118)	Metformin, Sulphonylurea, Thiazolidinedione	Initial dose of 10IU/day and titrated weekly to target FPG level $\leq 5.6$ mmol/L	5 $\mu$ g BD for the first 4 weeks and 10 $\mu$ g BD for the remainder of the study.	HbA1c Hypoglycaemia Weight
<b>Davies et al (2013)[24]</b>	Randomised, Open-label Parallel-arm, Controlled trial	222	Insulin detemir (105) Vs Exenatide (111)	Metformin +/- Sulphonylurea	Insulin detemir once or twice daily, titrated to FPG level $< 5$ mmol/L	2mg subcutaneous once weekly	-Proportion of achieving HbA1c $\leq 7$ mmol/L and weight $\geq 1.0$ kg -HbA1c -Hypoglycaemia
<b>de Wit et al (2014)[34]</b>	Randomised, Open-label Parallel-arm, Controlled trial	50	Insulin (24) Vs Liraglutide (26)	Metformin +/- Sulphonylurea	Standard therapy (continuation and intensification of insulin therapy without Liraglutide)	1.8mg/day	HbA1c Body weight
<b>Diamant et al (2010)[27]</b>	Randomised Open-label Controlled non-inferiority trial	456	Insulin glargine (223) Vs Exenatide (233)	Metformin +/- Sulphonylurea And others	Once daily injection, starting does 10IU, target glucose range between 4.0-5.5 mmol/L	2mg once a week injection	HbA1c Weight gain
<b>Diamant et al (2012)[26]</b>	Randomised Open-label Parallel-arm, Controlled trial	467	Insulin glargine (234) Vs Exenatide (233)	Metformin +/- Sulphonylurea	Once daily (10IU/day)	2mg once weekly	-Proportion of patients achieving HbA1c $< 7.0$ -Change in HbA1c
<b>Diamant et al (2014)[28]</b>	Randomised Open-label Controlled non-inferiority trial	627	Insulin Lispro (312) Vs Exenatide (315)	Insulin glargine and metformin	Thrice daily meal time dose titrated to pre-meal glucose of 5.6-6mmol/L.	5 $\mu$ g BD for the first 4 weeks and 10 $\mu$ g thereafter.	HbA1c Weight
<b>DIGAMI-2 (2011)[20]</b>	Randomised Open-label Blinded evaluation trial (post hoc analysis)	1253	Insulin (474) Vs INS + Non-INS GLT (473) Vs Non-INS GLT (304)	Not described	Short-acting insulin before meals and intermediate/long-acting insulin in the evening after 24-hr infusion of insulin and glucose.	Standard non-insulin GLTs given by a physician according to local routines after a 24-hr ins-glucose infusion.	Risk of all-cause mortality and CV events (including CV death)

<b>Dorkhan et al (2009)[29]</b>	Randomised Open-label Controlled trial (pilot study)	30	Insulin glargine (15) Vs Pioglitazone (15)	Metformin and Sulphonylurea	Insulin was up-titrated to achieve fasting plasma glucose <6mmol/l	Increased to 45mg/day after 16 weeks if HbA1c>6.2%	HbA1c, BMI
<b>Heine et al (2005)[30]</b>	Randomised Open-label Parallel-arm, Controlled trial	549	Insulin glargine (267) Vs Exenatide (282)	Metformin and Sulphonylurea	1 daily dose titrated to FPG level of less than 5.6mmol/L (<100mg/dl)	10 µg/day twice daily	HbA1c, Weight
<b>Matyjaszek-Matuszek et al (2013)[31]</b>	Randomised Open-label Parallel-arm, Controlled trial	80	Insulin glargine (40) Vs Exenatide (40)	Metformin and Sulphonylurea	10IU/day titrated with 2IU every 3 days (if needed) to achieve FPG <5.6mmol/L	5µg BD for 4 weeks, later increased to 10µg BD for the remaining trial period	HbA1c Body weight
<b>ORIGIN (2012)[19]</b>	Randomised Open-label Multi-centre trial	12,537	Insulin Glargine (6264) Vs Standard care (6273)	Glucose-lowering therapies (GLTs)	Insulin glargine	GLTs mainly metformin and sulphonylurea but never including Insulin glargine	CV events (including CV mortality) Weight
<b>Philis-Tsimikas et al (2013)[32]</b>	Randomised, open-label, parallel arm, Controlled trial	458	Insulin degludec (229) Vs Sitagliptin (229)	1-2 OADs (only among metformin, SU, Glinides or Pioglitazones)	10IU once daily titrated (if needed) to achieve FPG <5.0mmol/L	100mg orally once daily	HbA1c
<b>Rosenstock et al (2006)[33]</b>	Randomised, open-label, parallel arm, Controlled trial	219	Insulin glargine (105) Vs Rosiglitazone (112)	Metformin and Sulphonylurea	10units/day for 7 days with forced titrated to target FPG ≤5.5-6.7 mmol/L (≤100-120MG/dl)	4mg/day. Increased to 8mg/day any time after 6 weeks in FPG was >5.5mmol/l	HbA1c, Weight Hypoglycaemia

<sup>a</sup>Trial no: This includes only persons randomised to a treatment group

PG: Fasting Plasma Glucose;

<sup>b</sup>The list is not exhaustive. Only the outcome measures of interest were listed.

**Table 3: Commonest reported adverse drug events in Insulin vs Non-insulin groups**

Adverse Events	Number of Reported Events	
	Insulin, <i>n</i> (%)	Non-insulin, <i>n</i> (%)
Nasopharyngitis	239 (21.08)	246 (17.93)
Influenza	68 (6.00)	68 (4.96)
Mss/Back Pain	51 (4.50)	62 (4.52)
Headache	156 (13.76)	202 (14.72)
Gastrointestinal pain	37 (3.26)	108 (7.87)
Dizziness	18 (1.59)	34 (2.48)
Arthralgia	32 (2.82)	38 (2.77)
Diarrhoea	99 (8.73)	229 (16.69)
Infections-Infestations	62 (5.47)	55 (4.01)
Hypertension/AMI	15 (1.32)	14 (1.02)
Vomiting	36 (3.17)	177 (12.90)
Nausea	60 (5.29)	586 (42.71)
Constipation	25 (2.20)	67 (4.88)
Dyspepsia	19 (1.68)	81 (5.90)
Cough	61 (5.38)	40 (2.92)
Reduced Appetite	12 (1.06)	79 (5.76)
CNS Symptoms	38 (3.35)	29 (2.11)
Injection site reactions	4 (0.35)	64 (4.66)
<b>Total number of events</b>	<b>1134 (100)</b>	<b>1372 (100)</b>

Appendix: Figure 1.

These databases were electronically search using the using keywords, mesh headlines and terms as

"Diabetes Mellitus, Type 2/complications"[Mesh] OR "Diabetes Mellitus, Type 2/drug therapy"[Mesh] AND "Diabetes Mellitus, Type 2/epidemiology"[Mesh] OR "Diabetes Mellitus, Type 2/mortality"[Mesh] OR "Diabetes Mellitus, Type 2/prevention and control"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh] AND "insulin regime" OR "insulin schedule" OR insulin tim\* OR "insulin itinerary" OR insulin us\* OR insulin dose OR "insulin administration" OR insulin quantit\* OR "insulin shot" OR "insulin measure" AND "cardiovascular disease" OR "heart disease" OR macrovascular OR cardio\* OR "myocardial infarction" OR MI OR stroke OR cerebrovascular OR cerebro\* OR "major adverse cardiovascular event" OR "major adverse coronary event" OR MACE OR "all-cause mortality" AND "Randomized Controlled Trials".