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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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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 ⩽7.0% or 7.4% (53 or 57 mmol/mol) was similar in both (OR = 1.55; 95%CI = 0.92–2.62). 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: 1.44–2.51) 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.

1. Introduction

For many patients with type 2 diabetes (T2D), treatment intensification using additional antihyperglycemic 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

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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 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 RCTs involving patients with T2D.

2. Methods

2.1. 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 Fig. A1 of the Appendix.

2.2. 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 (Fig. 1).

2.3. 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.

2.4. 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