Effects on All-Cause Mortality and Cardiovascular Outcomes in Patients With Type 2 Diabetes by Comparing Insulin With Oral Hypoglycemic Agent Therapy: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Purpose: Retrospective, case–control studies and prospective randomized controlled trials (RCTs) on insulin treatment for diabetic patients yielded contradictory mortality and cardiovascular outcomes. We aimed to evaluate the effects of insulin versus oral hypoglycemic agents (OHAs) on all-cause mortality and cardiovascular outcomes in patients with type 2 diabetes (T2D).

Methods: We searched Medline, Embase, Cochrane Central Register of Controlled Trials, Chinese Biological Medicine Database, China National Knowledge Infrastructure, Chinese Technical Periodicals, and Wanfang Data, up to July 10, 2015, for RCTs on insulin and OHAs that assessed all-cause mortality and/or cardiovascular death as primary end points. We derived pooled risk ratios (RRs) as summary statistics.

Results: Three trials were included in which 7649 patients received insulin and 8322 received OHAs, with mean (SD) diabetes duration of 5.0 (6.2) and 4.4 (5.9) years, respectively. Insulin did not differ from OHAs in all-cause mortality (RR = 1.00; 95% CI, 0.93–1.07), cardiovascular death (RR = 1.00; 95% CI, 0.91–1.09), myocardial infarction (RR = 1.04; 95% CI, 0.93–1.16), angina (RR = 0.97; 95% CI, 0.88–1.06), sudden death (RR = 1.02; 95% CI, 0.66–1.56), or stroke (RR = 1.01; 95% CI, 0.88–1.15). Insulin reduced the risk of heart failure compared with OHAs (RR = 0.87; 95% CI, 0.75–0.99). In the subgroup of secondary prevention of cardiovascular diseases (CVDs) or very high risk of CVDs, insulin did not differ from OHAs in all-cause mortality (RR = 0.99; 95% CI, 0.92–1.07), cardiovascular death (RR = 0.99; 95% CI, 0.90–1.09), myocardial infarction (RR = 1.01; 95% CI, 0.88–1.15), heart failure (RR = 0.69; 95% CI, 0.34–1.40), or stroke (RR = 1.05; 95% CI, 0.90–1.21).

Implications: Insulin did not provide a clear benefit over OHAs in all-cause mortality or cardiovascular outcomes in the patients with T2D. Insulin therapy has many shortcomings, including inconvenience (injection, strict blood glucose monitoring), hypoglycemia, and obvious weight gain. Thus, we conclude that no robust evidence supports the active use of insulin for this population at present. (*Clin Ther.* 2015;∎:∎∎∎–∎∎∎)

Key words: all-cause mortality, cardiovascular outcomes, insulin, oral hypoglycemic agent, type 2 diabetes.

INTRODUCTION

The global estimate of adults with diabetes was 382 million in 2013. This number is expected to rise beyond 592 million by 2035.[1] Type 2 diabetes (T2D) is an important independent risk factor for cardiovascular disease (CVD). In fact, patients with diabetes have a 2-fold increase of hospital mortality and rate of CVDs compared with patients without diabetes.[2,3]

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Insulin and oral hypoglycemic agents (OHAs) are commonly used to lower blood glucose for T2D treatment. Some retrospective and prospective case–control studies of insulin treatment in diabetic patients have reported a higher prevalence of CVDs in insulin-treated patients.[3–8] However, in the sulfonylurea/insulin arms of the UK Prospective Diabetes Study (UKPDS), no difference was found in all-cause mortality and cardiovascular outcomes.[9] The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial found that insulin glargine did not differ significantly from the standard care.[10] Thus, the results of previous studies are contradictory.

Weight gain, hypoglycemia, need for injection, and strict blood glucose monitoring are associated with insulin therapy. Moreover, development of different types of OHAs has increased. Thus, insulin should be avoided if the target blood glucose can be achieved with OHAs, unless insulin proves to be more beneficial. All-cause mortality and cardiovascular outcomes are the most important prognostic indicators of diabetes. To clarify the different effects of insulin and OHAs on all-cause mortality and cardiovascular outcomes, we conducted a meta-analysis of randomized controlled trials (RCTs) to compare insulin with OHAs for patients with T2D.

METHODS

Information and Search Strategy

We searched for RCTs of insulin and OHAs through Medline (1950 to May 2015), Embase (1980 to May 2015), the Cochrane Central Register of Controlled Trials (1960 to May 2015), the Chinese Biological Medicine Database (1978 to May 2015, China National Knowledge Infrastructure (1994 to May 2015), Chinese Technical Periodicals (1989 to May 2015), and Wanfang Data (1998 to May 2015). The search key words used were as follows: "insulin and (oral hypoglycemic agent or oral hypoglycemic drug or oral anti-diabetic drug or oral anti-diabetic agent) and (T2D or Diabetes Mellitus, Type 2)." The Cochrane Highly Sensitive Search Filters for Randomized Trials were used.[11] We restricted the languages of articles to English and Chinese.

Study Eligibility and Selection

Inclusion criteria were as follows: RCTs that assessed all-cause mortality and cardiovascular outcomes of insulin versus OHA treatment (including standard care based on the investigator's judgment and local guidelines or clinical practices), participants with T2D, and follow-up duration >3 years. Exclusion criteria were as follows: cross-over trials, studies without data on all-cause mortality or cardiovascular outcomes, and studies in which OHAs were discontinued because of severe adverse effects or OHAs are no longer used clinically. The identified records were managed by EndNote reference management software version X7 (Thomson Reuters, Columbus, Ohio). Two reviewers (J.L. and Y.T.) independently reviewed the abstracts and full-text articles to determine the eligibility of the studies for inclusion in the meta-analysis. Disagreements were resolved by consensus or by the opinion of a third reviewer.

Risk of Bias Assessment and Data Extraction

We assessed the risk of bias in the included studies with the use of the Cochrane Collaboration's tool,[11] which detects selection, performance, detection, attrition, and reporting bias and categorizes risk of bias as low, high, or unclear. Studies with high risk of bias were excluded from the meta-analysis.

We used a self-designed data extraction form to abstract study characteristics and outcomes. Recorded study characteristics included design, population, number of patients, participant baseline characteristics, and follow-up. The primary end points were all-cause mortality and cardiovascular death. The secondary end points were cardiovascular events, including myocardial infarction, stroke, heart failure, sudden death, and angina. We used the cardiovascular death definition from the ORIGIN trial.[10] The definitions of the other end points included correspond to those reported in the originally published papers. Because not all the studies reported the same end points, evaluations were not always based on the overall study population.

The same two reviewers (J.L. and Y.T.) independently assessed the risk of bias in the retrieved studies and performed the extraction of outcome and trial characteristic data from the published articles and appendices. Any disagreements were resolved by reviewing the original data or consulting between the reviewers.

Data Synthesis and Statistical Analysis

The analyses were performed with Review Manager Software (version 5.3; Cochrane Collaboration, London, United Kingdom). We used risk ratios (RRs) and 95% CIs as summary statistics for dichotomous variables. These were calculated from the number of