Legacy Effect of Intensive Blood Glucose Control on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Very High Risk or Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Purpose: We performed a meta-analysis to investigate the legacy effect of >5 years of intensive blood glucose lowering on cardiovascular outcomes in patients with type 2 diabetes and very high risk or secondary prevention of cardiovascular disease (CVD).

Methods: We mainly searched PubMed, Embase, and the Cochrane Library for relevant randomized controlled trials. Patients in the included studies had intensive glucose lowering for >5 years and posttrial follow-up for at least 5 years. Primary end points were all-cause mortality and cardiovascular death. Secondary end points were major macrovascular events, myocardial infarction, and stroke. We used risk ratios (RRs) with 95% CIs as summary statistics.

Findings: We included 3 trials that involved 13,684 patients, of whom 6805 received intensive glucose-lowering treatment and 6879 received standard treatment. The mean total follow-up duration was 10.3 years, which included 5.4 years of in-trial intervention and 5.5 years of posttrial follow-up. Intensive glucose control treatment did not significantly reduce all-cause mortality (RR = 0.98; 95% CI, 0.87–1.10) or cardiovascular death (RR = 0.97; 95% CI, 0.87–1.09). No significant risk reduction was found for stroke (RR = 1.02; 95% CI, 0.92–1.14), myocardial infarction (RR = 0.91; 95% CI, 0.75–1.09), or major macrovascular events (RR = 0.99; 95% CI, 0.93–1.06).

Implications: A legacy effect of >5-year intensive blood glucose control on cardiovascular outcomes in patients with type 2 diabetes and very high risk or secondary prevention of CVD was not detected, although this effect might be applicable in patients with diabetes and primary prevention of CVD. Further investigation of the legacy effect in different CVD risk populations should therefore be performed. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: cardiovascular diseases, intensive blood glucose control, legacy effect, secondary prevention, type 2 diabetes mellitus.

INTRODUCTION

Diabetes is a serious and increasing public health concern that results in reduced life quality and increased mortality. Patients with type 2 diabetes mellitus (T2DM) have a greatly increased risk of cardiovascular disease (CVD), the leading cause of death in this population. The primary prevention of CVD in patients with T2DM is defined as preventing the occurrence of CVD in patients without clinical CVD. Secondary prevention is defined as preventing CVD from recurrence, reducing mortality and lethality, and improving the life quality of patients with T2DM. Moreover, patients with diabetes are considered at high risk of CVD, and patients with diabetes and other risk factors (eg, hypertension, obesity, smoking, and dyslipidemia) for CVD are considered at very high risk of CVD.[1]

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Intensive blood glucose control used to be recommended as a therapeutic strategy to decrease the incidence of vascular complications.[2] The definition of intensive blood glucose control is relative to that of standard blood glucose control. Intensive blood glucose control is defined as high-intensity treatment in specified glycated hemoglobin (HbA_{1c}), fasting glucose, or postprandial glucose targets with insulin or oral hypoglycemic agents, whereas standard blood glucose control is nonintensification treatment in HbA_{1c}, fasting glucose, or postprandial glucose targets with placebo or low dosage of oral hypoglycemic agents or insulin. Several large randomized controlled trials (RCTs) have been conducted to investigate the effect of intensive blood glucose control on cardiovascular events in T2DM. There is clear evidence that intensive blood glucose control can reduce the risk of microvascular disease, but for macrovascular outcomes, the evidence is less well established.[3]

The United Kingdom Prospective Diabetes Study (UKPDS) 33 found that patients with T2DM in the intensive blood glucose control group had a substantially decreased risk of microvascular complications.[4] In the UKPDS 80 study, the 10-years posttrial follow-up of UKPDS, a continued reduction in microvascular risk and emergency risk reductions for myocardial infarction (MI) and death from any cause were found and termed the *legacy effect*, indicating that a long-term intensive strategy to control blood glucose levels in patients with T2DM produced sustained effects on microvascular and macrovascular outcomes after the cessation of intensive interventions. This phenomenon was observed despite the early loss of within-trial differences in HbA_{1c} levels between the intensive-therapy and standard-therapy groups.[5]

However, evidence for such a legacy effect of intensive blood glucose control on cardiovascular events in T2DM is conflicting among different RCTs. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, no evidence indicated that 5-year intensive glucose control during the trial led to long-term benefits, with respect to mortality or macrovascular events.[6] The Veterans Affairs Diabetes Trial (VADT) study found a 17% relative reduction in the rate of major cardiovascular events with approximately 5 years of intensive therapy, but no improvement in the rate of overall survival was observed after a total follow-up of almost 12 years.[7] Most hypoglycemic trials enrolled not only patients with T2DM and secondary prevention of CVD but also patients with very high risk and secondary prevention of CVD together. Because the data could not be distinguished between the 2 groups in these trials, we considered them as the same group, described as patients with very high risk or secondary prevention of CVD. We conducted a meta-analysis to summarize and assess the available evidence of whether intensive blood glucose control had long-term benefits on cardiovascular outcomes in patients with T2DM and very high risk or secondary prevention of CVD.

METHODS

Protocol and Registration

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement and was registered at International Prospective Register of Systematic Reviews (CRD42016044126).

Electronic Searches

We searched PubMed, Embase, and the Cochrane Central Register Controlled Trials for articles published until March 2017. Keywords and their synonyms were used to sensitize the search. The search keywords were as follows: *diabetes mellitus, type 2*; *blood glucose*; *hypoglycemic agents*; and *tight* or *intensive* or *strict*. The Cochrane Highly Sensitive Search Strategy for RCTs was used.[8] We also searched ClinicalTrials.gov and conference proceedings to identify additional eligible studies. Furthermore, we supplemented the electronic search from reference lists of relevant articles, including meta-analyses and reviews.

Study Eligibility and Selection

The inclusion criteria for this meta-analysis were as follows: (1) prospective RCTs; (2) trials that enrolled patients with T2DM and very high risk or secondary prevention of CVD (patients with T2DM and anyone of other risk factors, such as hypertension, obesity, smoking, and dyslipidemia, or patients with T2DM and established CVD); (3) trials randomly assigning patients to low versus high HbA_{1c}, fasting glucose or postprandial glucose targets (intensive vs standard