# A systematic review and meta-analysis of glycemic control for the prevention of diabetic foot syndrome

**Rim Hasan, MD,[a,b] Belal Firwana, MD,[a,b] Tarig Elraiyah, MBBS,[a] Juan Pablo Domecq, MD,[a,c] Gabriela Prutsky, MD,[a,c] Mohammed Nabhan, MD,[a] Larry J. Prokop, MLS,[d] Peter Henke, MD,[e] Apostolos Tsapas, MD, PhD,[f] Victor M. Montori, MD, MSc,[a,g]** and **Mohammad Hassan Murad, MD, MPH,[a,h]**
*Rochester, Minn; Columbia, Mo; Lima, Peru; Ann Arbor, Mich; and Thessaloniki, Greece*

***Objective:*** **The objective of this review was to synthesize the available randomized controlled trials (RCTs) estimating the relative efficacy and safety of intensive vs less intensive glycemic control in preventing diabetic foot syndrome.**
***Methods:*** **We used the umbrella design (systematic review of systematic reviews) to identify eligible RCTs. Two reviewers determined RCT eligibility and extracted descriptive, methodologic, and diabetic foot outcome data. Random-effects meta-analysis was used to pool outcome data across studies, and the $I^2$ statistic was used to quantify heterogeneity.**
***Results:*** **Nine RCTs enrolling 10,897 patients with type 2 diabetes were included and deemed to be at moderate risk of bias. Compared with less intensive glycemic control, intensive control (hemoglobin $A_{1c}$, 6%-7.5%) was associated with a significant decrease in risk of amputation (relative risk [RR], 0.65; 95% confidence interval [CI], 0.45-0.94; $I^2 = 0\%$). Intensive control was significantly associated with slower decline in sensory vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79). There was no effect on other neuropathic changes (RR, 0.89; 95% CI, 0.75-1.05; $I^2 = 32\%$) or ischemic changes (RR, 0.92; 95% CI, 0.67-1.26; $I^2 = 0\%$). The quality of evidence is likely moderate.**
***Conclusions:*** **Compared with less intensive glycemic control therapy, intensive control may decrease the risk of amputation in patients with diabetic foot syndrome. The reported risk reduction is likely overestimated because the trials were open and the decision to proceed with amputation could be influenced by glycemic control. (J Vasc Surg 2016;63:22S-28S.)**

Diabetic foot syndrome arises from either vasculopathic or neuropathic complications of diabetes.[1] Prevalence varies from 3% to 30% among patients with diabetes.[2] Diabetic foot syndrome leads to an ulcer in 10% to 30% of patients.[3-5] It increases the risk of amputation by 8- to 23-fold and increases mortality rates in patients with diabetes.[3-5] Complicated foot ulcers represent a major reason for hospitalization, amputation, and utilization of health care resources.[1]

It has been postulated that chronic hyperglycemia is associated with microvascular and macrovascular changes that play a role in diabetic foot disease.[6,7] However, it is yet unclear whether lowering glucose to normal or nearly normal targets (intensive glycemic control) leads to reduction in the incidence of diabetic foot syndrome (ie, prevention of diabetic foot). This hypothesis has been tested in several randomized controlled trials (RCTs) that reported variable findings. The United Kingdom Prospective Diabetes Study (UKPDS)[7] concluded that intensive control had a favorable effect on the incidence of microvascular complications and diabetic foot but not on macrovascular disease. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[8] showed similar effect on microvascular events but reported an increase in total and cardiovascular-related mortality and increased weight gain. The Veterans Affairs Cooperative Study on type 2 diabetes mellitus (VA CSDM)[9] demonstrated that intensive control had no significant effect compared with conventional control, and it did not decrease the overall prevalence of peripheral neuropathy.

Therefore, we conducted this systematic review and meta-analysis to appraise and to summarize the randomized trial evidence regarding the impact of intensive glycemic control on the incidence of amputation and other diabetic foot syndrome outcomes.

## METHODS

Because glycemic control can be achieved by multiple interventions and in multiple settings and because its effect has been evaluated previously in multiple systematic reviews, we used an umbrella systematic review approach.

From the Evidence-based Practice Center,[a] Mayo Clinic Libraries,[d] Division of Endocrinology, Diabetes, Metabolism, and Nutrition,[g] and Division of Preventive, Occupational and Aerospace Medicine,[h] Mayo Clinic, Rochester; the Department of Internal Medicine, University of Missouri, Columbia[b]; the Unidad de Conocimiento y Evidencia (CONEVID), Lima[c]; the Department of Surgery, University of Michigan Medical School, Ann Arbor[e]; and the Second Medical Department, Aristotle University Thessaloniki, Thessaloniki.[f]
This review was partially funded by a contract from the Society for Vascular Surgery.
Author conflict of interest: none.
Additional material for this article may be found online at www.jvascsurg.org.
Correspondence: Mohammad Hassan Murad, MD, MPH, Evidence-based Practice Center, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: murad.mohammad@mayo.edu).
Independent peer review and oversight have been provided by members of the Society for Vascular Surgery Document Oversight Committee: Peter Gloviczki, MD (Chair), Martin Bjorck, MD, Ruth Bush, MD, Thomas Forbes, MD, Michel Makaroun, MD, and Gregory Moneta, MD.
0741-5214

http://dx.doi.org/10.1016/j.jvs.2015.10.005

In brief, this approach starts with identifying relevant systematic reviews that compared intensive glycemic control with less intensive control. Eligible systematic reviews are retrieved (regardless of intervention and regardless of whether diabetic foot was an outcome of interest) and are used to identify relevant RCTs. RCTs are subsequently retrieved and undergo quality appraisal, data extraction, and meta-analysis of relevant outcomes.

**Information sources and search methods.** A comprehensive literature search was conducted by an expert reference librarian with input from study investigators with experience in systematic reviews (V.M.M. and M.H.M.). We searched the electronic databases (MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials [CENTRAL]) for systematic reviews using various combinations of controlled vocabulary supplemented by keywords for the concepts of prevention and diabetic foot. Results were limited to systematic reviews. The full search strategy is reported in the Appendix (online only).

Two reviewers working independently identified systematic reviews eligible for further review by performing a screen of abstracts and titles. If a systematic review was deemed relevant, the manuscript was obtained and reviewed in full-text versions. The included RCTs from the reviewed systematic reviews were retrieved in full-text versions (all available versions of each study) for further assessment.

**Eligibility criteria.** We included RCTs that enrolled patients with diabetes (of any type) without diabetic foot ulcers, comparing intensive glycemic control against less intensive glycemic control and evaluating the incidence of diabetic foot syndrome. The outcomes of interest were amputation and the incidence of diabetic foot, defined as a new ulcer, gangrene, or other forms of neuropathic or ischemic changes.

**Risk of bias assessment.** We used the Cochrane risk of bias tool to evaluate the methodologic quality of RCTs. Two reviewers independently assessed trial quality by examining several components: generation of allocation sequence (classified as adequate if based on computer-generated random numbers, tables of random numbers, or similar), concealment of allocation (classified as adequate if based on central randomization, sealed envelopes, or similar), blinding (patients, caregivers, or outcome assessors), baseline imbalance, adequacy of follow-up, and source of funding (whether it is only by not-for-profit sources or includes for-profit source). Disagreements between the reviewers were resolved by discussion or arbitrated with a third reviewer (M.H.M.). The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[10,11] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty) and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

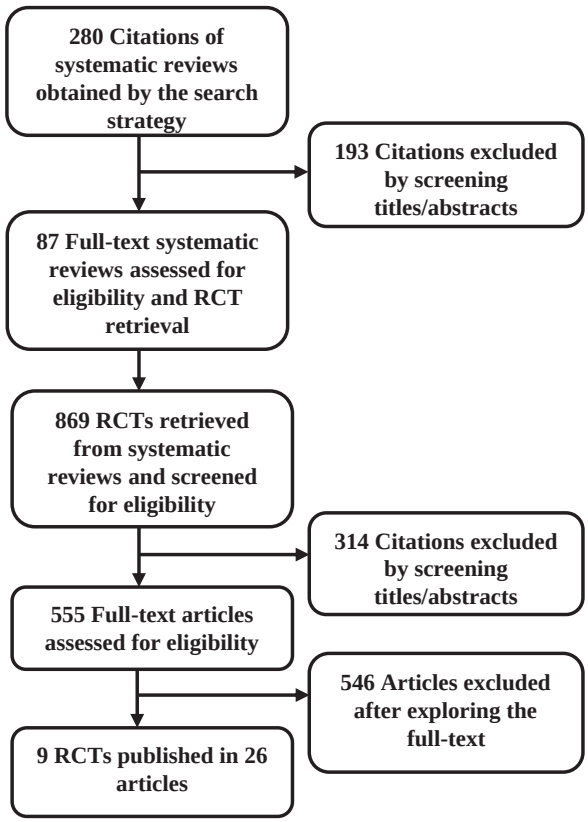


**Fig 1.** The process of study selection. *RCTs,* Randomized controlled trials.

**Data collection and extraction.** The data from RCTs were extracted using a standardized, piloted, and web-based data extraction form and working in duplicates. We abstracted data on patient demographics, baseline characteristics, study design, sample size, intervention type, fasting blood glucose and hemoglobin $A_{1c}$ levels, and diabetic foot outcome measures. The number of events in each trial was extracted, when available, and attributed to the arm to which patients were randomized (ie, the basis of the intention-to-treat approach). When change-from-baseline standard deviations for an outcome were not available, they were imputed from other studies in the review. When a study reported follow-up at different periods, outcomes with the longest follow-up were extracted.

**Statistical analysis and data synthesis.** We estimated the relative risk (RR) and the mean difference with the associated 95% CIs and pooled across studies using a random-effects model, as described by DerSimonian and Kacker.[12] We chose the random-effects method as primary analysis because of its conservative summary estimate and incorporation of between- and within-study variance. The analysis was repeated using the fixed-effect method, and discrepancies, if present, were outlined. To assess