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

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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.

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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]).

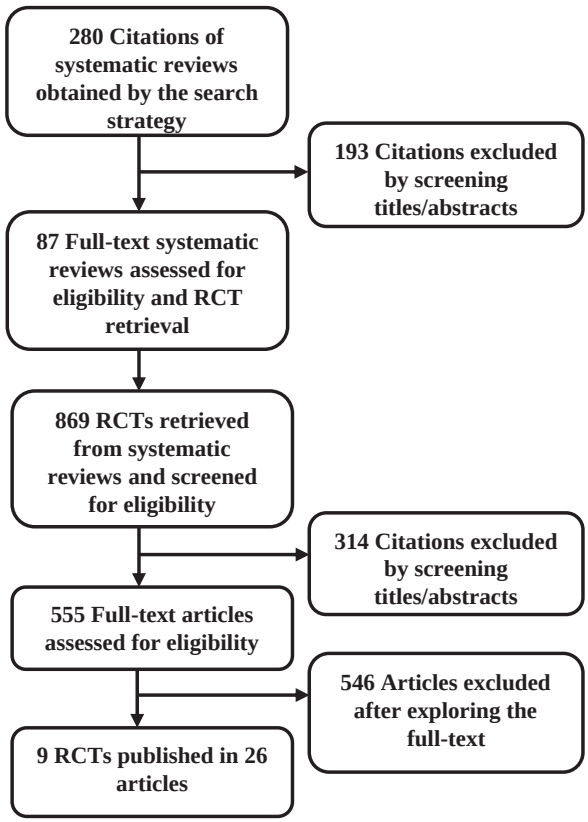

Fig 1. The process of study selection. *RCTs,* Randomized controlled trials.

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

Table I. Trial description and baseline characteristics

Trial	*Origin*	*No. of subjects*	*Follow-up, months*	*Duration of DM, years*	*Male, No. (%)*	*Age, years*	*Target in intensive group*	*Fasting glucose, mg/dL*		*HbA$_{1c}$, %*	
								At entry	*Achieved*	*At entry*	*Achieved*
VADT,[19] 2009	United States	1791	67.2	11.5	1737 (97)	61 ± 9	HbA$_{1c}$ <6%	—	—	I: 9.4 C: 9.4	I: 6.9 C: 8.4
Steno-2,[20] 2008	Denmark	160	46	I: 5.5 C: 6	118 (74)	55	HbA$_{1c}$ <6.5%	I: 182 C: 189	I: 130 C: 178	I: 8.4 C: 8.8	I: 7.9 C: 9.0
Holman,[21] 1983	United Kingdom	74	24	19	67 (64)	42 ± 12	PPG: 72-126	—	—	I: 11.7 C: 11.8	I: 10.5 C: 11.4
UKPDS,[7] 1998	United Kingdom	4209	120	0	2516 (60)	I: 53 ± 9 C: 53 ± 9	FPG <108	I: 146 C: 144	I: 155 C: 177	I: 7.1 C: 7.1	I: 8.1 C: 8.7
Abraira,[18] 1997 (VA CSDM)	United States	153	27	7.8	153 (100)	60 ± 6	HbA$_{1c}$ <7.5%	I: 207 C: 225	I: 103 C: 206	I: 9.3 C: 9.5	I: 7.1 C: 9.6
Ohkubo,[23] 1995	Japan	110	72	8.5	54 (49)	50 ± 16	HbA$_{1c}$ <7%	I: 165 C: 170	I: 125 C: 170	I: 9.2 C: 9.0	I: 7.1 C: 9.6
UGDP,[22] 1978	United States	619	120	1	177 (29)	53 ± 11	FPG <110	C: 143 I: 138	C: 166 I: 122	—	—
ADDITION-Europe,[16] 2011	United Kingdom and Denmark	3057	64		57	60	HbA$_{1c}$ <7%	—	—	I: 7.0 C: 7.0	I:6.6 C: 6.7
Araki,[17] 2012	Japan	1133	72	18	46	72	HbA$_{1c}$ <6.9%	170	—	8.5	I: 7.7 C: 7.8

C, Control; *DM*, diabetes mellitus; *FPG*, fasting plasma glucose; *HbA$_{1c}$*, hemoglobin A$_{1c}$; *I*, intervention; *PPG*, postprandial glucose.

heterogeneity of treatment effect among trials, we used the I^2 statistic; the I^2 statistic represents the proportion of heterogeneity of treatment effect across trials that is not attributable to chance or random error. Hence, a value of 50% reflects significant heterogeneity that is due to real differences in study populations, protocols, interventions, or outcomes.[13] The *P* value threshold for statistical significance was set at .05 for effect sizes. Analyses were conducted using features on RevMan version 5.1 (The Nordic Cochrane Center, Copenhagen, Denmark). The study was reported in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) work groups.[14]

RESULTS

Search results and study description. A total of 280 systematic reviews were identified by the electronic search strategy, of which 87 full-text articles met the eligibility for assessment. All RCTs included in eligible systematic reviews, whether their outcomes were pooled in a meta-analysis or not, were retrieved and screened for eligibility. A recent Cochrane systematic review[15] identified two RCTs[16,17] published after our search that we added to analysis. A total of nine RCTs, reported in 26 published manuscripts at different follow-up points, met the inclusion criteria.[7,16-23] We excluded several RCTs that are well known in this field. For the lack of planned glycemic control target, we excluded PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive][24] and the Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy trial (ADOPT).[25] For the lack of reporting amputation outcome, we excluded the ACCORD trial,[8] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[6] and the RCT by Service et al.[26]

Fig 1 depicts the results of the search strategy, and Table I describes the included studies.

The nine trials enrolled 10,897 patients with diabetes. In these trials, patients were observed for a period of 2 years to 10 years (median, 5 years). Mean age ranged from 41 to 72 years; duration of diabetes before enrollment ranged from newly diagnosed to 19 years. The RCTs aimed for different glycemic targets for the intensive and the less intensive control arms. The goal of glycemic control was based on fasting glucose concentration of <126 mg/dL in the older trials and hemoglobin A$_{1c}$ (6%-7.5%) in more recent trials. Most included trials enrolled patients without known history of peripheral vascular disease who are at lower risk for amputation. All the trials that evaluated the outcome of amputation enrolled patients with type 2 diabetes (none with type 1). In Table I, we describe the characteristics of the trials; in Table II, we describe the intervention and control employed in each trial.

The standard domains of the risk of bias (Table III) were all adequate and consistent with low risk of bias with the exception of a concern about whether the decision to amputate was associated with the assignment to the intervention. It is plausible that patients with suboptimal control were more likely to be advised to proceed with amputation. Therefore, this evidence likely warrants moderate confidence.

Table II. Interventions used in included trials

Study ID	*Intensive arm*	*Conventional arm*
VADT,[19] 2009	Metformin plus rosiglitazone if BMI ≥27; glimepiride plus rosiglitazone if BMI <27; insulin was added if HbA_{1c} >9%. Patients started on the maximal dose.	Metformin plus rosiglitazone if BMI ≥27; glimepiride plus rosiglitazone if BMI <27; insulin was added if HbA_{1c} >9%. Patients started on half the maximal dose.
Steno-2,[20] 2008	If patients were unable to maintain HbA_{1c} <6.5% by means of diet and increased physical activity alone after 3 months, an oral hypoglycemic agent was started: • Overweight patients (BMI >25) received metformin (maximum, 1 g twice daily). • Lean patients, or overweight patients who had contraindications to metformin therapy, received gliclazide (maximum, 160 mg twice daily). • As the second step, metformin was added to the regimen of lean patients and gliclazide to that of overweight patients if hyperglycemia was not controlled. If the HbA_{1c} exceeded 7.0% despite maximal doses of oral agents, the addition of NPH insulin at bedtime was recommended. The insulin dose was adjusted on the basis of the morning fasting blood glucose concentration.	Treatment according to the 1988 recommendations of the Danish Medical Association
Holman,[21] 1983	Patients used ultralente insulin as basal cover and soluble insulin at mealtimes; mean insulin dose, 0.77 ± 0.30 IU/kg	Patients continued their usual therapy; mean insulin dose, 0.81± 0.29 IU/kg
UKPDS,[7] 1998	Treatment with one of the following three agents was initiated: • One of the following sulfonylureas: chlorpropamide 100-500 mg, glibenclamide 2.5-20 mg, or glipizide 2.5-40 mg • Metformin up to 2550 mg, distributed in two doses a day • Insulin started on once-daily ultralente insulin or isophane insulin. If the daily dose was >14 U or premeal or bedtime home blood glucose measurements were >7 mmol/L, a short-acting insulin, usually soluble (regular) insulin, was added (basal/bolus regimen). All participants had to continue their assigned treatment as long as possible. Patients were changed to insulin therapy if marked hyperglycemia recurred.	Patients were treated initially with dietary modification. If marked hyperglycemia or symptoms occurred, patients were secondarily randomized to treatment with sulfonylurea or insulin or metformin therapy. The aim of fasting plasma glucose <15 mmol/L without symptoms was maintained.
Abraira,[18] 1997 (VA CSDM)	*Phase 1*: one injection of intermediate- or long-acting insulin in the evening. *Phase 2*: continued evening insulin with the addition of glipizide in step increment of 2.5 to 5 mg/wk until HbA_{1c} goal is achieved or the maximum dose is reached. *Phase 3*: discontinue glipizide and give two insulin injections a day. *Phase 4*: multiple daily injections.	One daily injection of insulin; if goal not achieved, a maximum of two daily insulin injections are given.
Ohkubo,[23] 1995	Administered insulin three or more times daily (rapid-acting insulin at each meal and intermediate-acting insulin at bedtime)	One or two daily intermediate-acting insulin injections
UGDP,[22] 1978	Insulin variables (U-80 Lente or other insulin)	Standard insulin (U-80 Lente Iletin insulin)
ADDITION-Europe,[16] 2011	Target of HbA_{1c} <7%, but change in antidiabetic medicine with HbA_{1c} >6.5%	Standard care
Araki,[17] 2012	Oral hypoglycemic drugs (sulfonylurea, biguanides, α-glucosidase inhibitors, and pioglitazone) or insulin therapy	Oral hypoglycemic agents/ standard care

BMI, Body mass index; *HbA_{1c}*, hemoglobin A_{1c}.

Meta-analysis. Compared with less intensive glycemic control, intensive control was associated with a statistically significant decrease in risk of amputation of diabetic foot (RR, 0.65; 95% CI, 0.45-0.94; I^2 = 0%). Results are depicted in Fig 2.

Two studies reported on sensory nerve function,[21,23] in which a measurement of the changes in vibration threshold from baseline was used. The pooled result showed, when using the fixed-effect model, that compared with conventional control, intensive control

Table III. Quality assessment and risk of bias

Study ID	*Randomization*	*Allocation concealment*	*Blinding*	*Baseline imbalances*	*Lost to follow-up, %*	*Source of funding*
VADT,[19] 2009	Yes; permuted-block design	Yes; study sites did not have access to patient codes	Yes; patients and caregivers	No	6.4	Includes for-profit sources
Steno-2,[20] 2008	Yes; method unclear	Yes; sealed envelopes	Yes; outcome assessors	No	6.8	Not-for-profit sources
Holman,[21] 1983	Yes; method unclear	Yes; sealed envelopes	Unclear	No	6.8	Not-for-profit sources
UKPDS,[7] 1998	Yes; computer generated	Yes; sealed envelopes	Yes; outcome assessors	No	None	Not-for-profit sources
Abraira,[18] 1997 (VA CSDM)	Unclear	Unclear	Unclear	No	None	Not-for-profit sources
Ohkubo,[23] 1995	Unclear	Unclear	Unclear	No	2.7	Not-for-profit sources
UGDP,[22] 1978	Yes; tables of random numbers	Yes; method unclear	Yes; outcome assessors and data analyst	No	0	Not-for-profit sources
ADDITION-Europe,[16] 2011	Yes, cluster randomization	Yes	Outcome assessors	No	Unclear	Includes for-profit sources
Araki,[17] 2012	Adequate	Yes	Outcome assessors	No	9	Not-for-profit sources

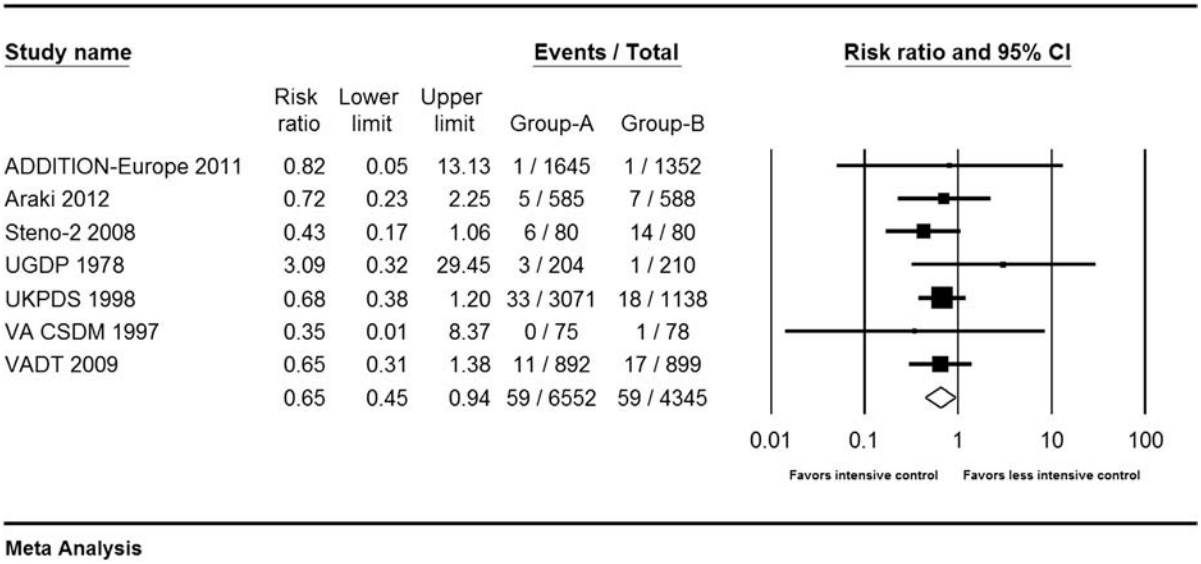

Fig 2. The risk of amputation. Group A, intensive control arm. Group B, conventional control arm. *CI,* Confidence interval.

caused a significant decrease (ie, less increase) in vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79), which means a better sensory nerve function outcome. The risk of neuropathic changes (RR, 0.89; 95% CI, 0.75-1.05; I^2 = 32%) and ischemic changes (RR, 0.92; 95% CI, 0.67-1.26; I^2 = 0%) associated with intensive glycemic control was not statistically significant (Supplementary Figs 1 and 2, online only). Ischemic changes were a heterogeneous outcome defined differently across trials (gangrene, ischemic ulcer, new-onset claudication, new diagnosis of peripheral artery disease). In metaregression, there was no significant association between the relative effect on amputation and the baseline risk for amputation in the control arms of the RCTs ($P > .05$). The small number of RCTs did not allow additional subgroup analyses or statistical evaluation for publication bias.

DISCUSSION

We conducted a systematic review and meta-analysis comparing intensive glycemic control with less intensive glycemic control for the prevention of diabetic foot. Intensive control was associated with decreased risk of amputation, better sensory nerve function, and potentially overall diabetic foot incidence. The quality of evidence is likely moderate, considering that these are open trials and the

decision to proceed with amputation may be associated with diabetes control, thus biasing the results toward favoring intensive glycemic control. Further, we were not able to assess certain confounders, such as baseline comparators of limb perfusion (eg, ankle-brachial index or toe-brachial index), medication use such as antiplatelet therapy, and personal habits of consistent foot hygiene. Most included trials enrolled patients without known history of peripheral vascular disease. The effect of diabetes control in patients with established peripheral vascular disease may be different, as these patients may be less responsive to intensive glucose control.

The observed RR reduction of 35% may indeed be too optimistic, considering the impact of other interventions, such as statins, smoking cessation, and blood pressure control. Intensive glycemic control may not improve patients' quality of life measures[27,28] and can be associated with increased treatment burden (more drugs, higher doses, more side effects, higher cost, more laboratory testing and visits to physicians). Thus, clinicians need to assess the capacity of the patient and the patient's caregivers to implement these complex programs.[29] Weight gain and hypoglycemia are common side effects associated with intensive control of type 2 diabetes.

Our results are consistent with those of a recent systematic review[15] of RCTs conducted by the Cochrane Collaboration. Our results are also consistent with a systematic review of observational prospective epidemiologic studies[30] that found a 1.26 RR (95% CI, 1.16-1.36) for each percentage point increase in hemoglobin A_{1c} to be associated with lower extremity amputation. The estimated RR was 1.44 (95% CI, 1.25-1.65) for type 2 diabetes and 1.18 (95% CI, 1.02-1.38) for type 1 diabetes; however, the difference was not statistically significant ($P = .09$).[30]

The strengths of this review stem from the comprehensive literature search that follows an explicit protocol and bias protection measures undertaken by reviewers (such as selecting studies, evaluating quality of the studies, and extracting outcome data by two independent reviewers). The weaknesses stem from inability to evaluate patient-level covariates that are needed to conduct meaningful subgroup analyses, such as cardiovascular risk factor control, use of statins and aspirin, age, and other comorbidities (eg, lower extremity edema). Such analyses may demonstrate differential benefit of an approach of intensive glycemic control.

The Society for Vascular Surgery is planning to develop clinical practice guidelines for the management of diabetic foot syndrome. A panel of experts will use data from this report and other sources of evidence and incorporate additional relevant aspects, such as patients' values and preferences, resource allocation, and clinical context, to develop clinical recommendations. A key factor in the recommendation for strict diabetes control is the need for it to be balanced with the potential for important hypoglycemia, the patient's capacity to achieve the glycemic control, and the risk of other outcomes, such as stroke and cardiovascular events, that can be associated with strict control of type 2 diabetes.

CONCLUSIONS

Compared with less intensive glycemic control therapy, intensive control decreases 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.

AUTHOR CONTRIBUTIONS

Conception and design: RH, BF, TE, JD, AT, LP, GP, MN, VM, MM
Analysis and interpretation: RH, MM
Data collection: RH, BF, TE, JD, AT, LP, GP, MN, MM
Writing the article: RH, LP, GP, VM, MM
Critical revision of the article: RH, BF, TE, JD, AT, LP, GP, MN, MM
Final approval of the article: RH, BF, TE, JD, AT, LP, GP, MN, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: diabetes control, limited to systematic reviews.

The actual search strategy

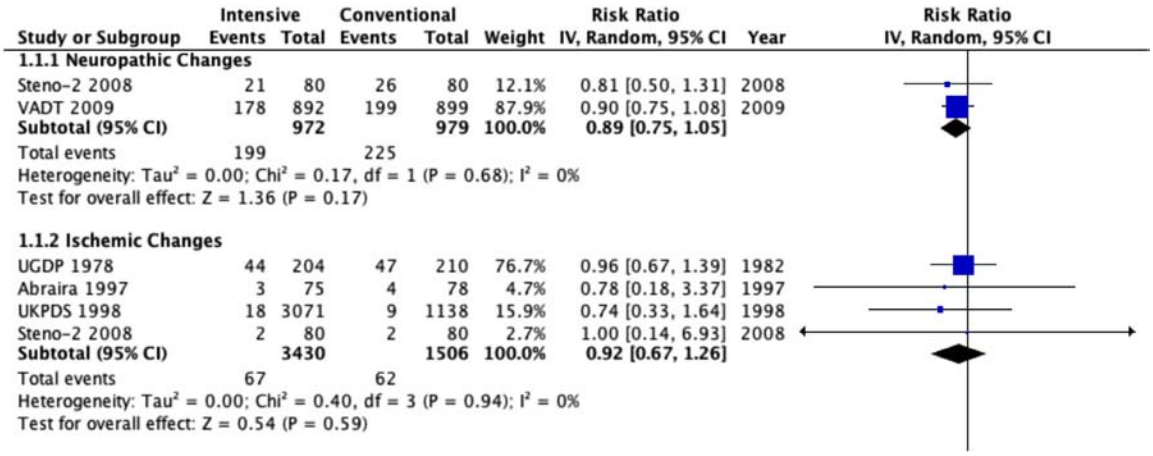
Ovid. Databases: Embase 1988 to 2011 Week 41, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

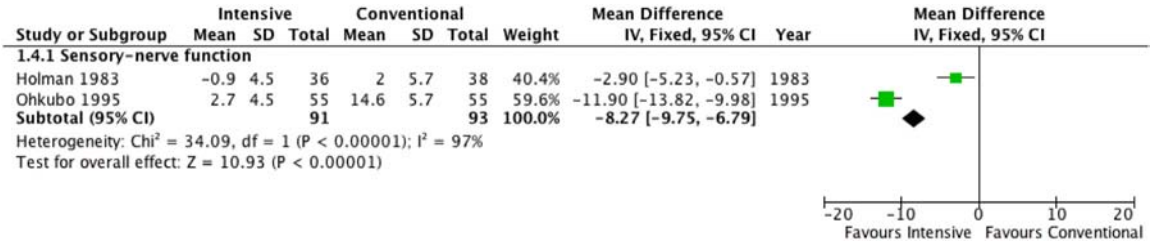
#	*Searches*	*Results*
1	exp Diabetes Mellitus/pc [Prevention & Control]	33286
2	(control or controls or controlling).ti,ab.	3743841
3	1 and 2	8728
4	(diabetes adj3 (control or controls or controlling)).ti,ab.	15376
5	exp "systematic review"/	44283
6	(systematic* adj2 review*).mp.	106172
7	3 or 4	22638
8	5 and 7	148
9	6 and 7	323
10	from 9 keep 203-323	121
11	from 7 keep 22621-22638	18
12	8 or 10 or 11	271
13	remove duplicates from 12	234
14	limit 13 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CDSR; records were retained]	22
15	13 not 14	212
16	11 or 15	230

Scopus.

1) TITLE-ABS-KEY((control w/3 diabetes) or (controls w/3 diabetes) or (controlling w/3 diabetes))
2) TITLE-ABS-KEY(systematic* w/2 review*)
3) 1 and 2
4) PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
5) 3 and not 4
6) DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
7) 5 and not 6



Supplementary Fig 1 (online only). The risk of neuropathic and ischemic changes. *CI*, Confidence interval; *IV*, information value.



Supplementary Fig 2 (online only). Neuropathy; changes in vibration threshold (fixed-effect model). *CI*, Confidence interval; *IV*, information value; *SD*, standard deviation.