Systematic Review: Glucose Control and Cardiovascular Disease in Type 2 Diabetes

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Background: Results from clinical trials examining the effect of intensive glucose control on cardiovascular disease have been conflicting.

Purpose: To summarize clinical benefits and harms of intensive versus conventional glucose control for adults with type 2 diabetes.

Data Sources: Studies were retrieved by systematically searching the MEDLINE database (January 1950 to April 2009) with no language restrictions.

Study Selection: Two independent reviewers screened abstracts or full-text articles to identify randomized trials that compared clinical outcomes in patients with type 2 diabetes receiving intensive glucose control and those receiving conventional glucose control.

Data Extraction: Two investigators independently abstracted data on study variables and outcomes, including severe hypoglycemia, cardiovascular disease, and all-cause mortality.

Data Synthesis: 5 trials involving 27 802 adults were included. Intensive glucose targets were lower in the 3 most recent trials. Summary analyses showed that compared with conventional control, intensive glucose control reduced the risk for cardiovascular disease (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]; risk difference per 1000 patients per 5 years [RD], −15 [CI, −24 to −5]) but not cardiovascular death (RR, 0.97 [CI, 0.76 to 1.24]; RD, −3 [CI, −14 to 7]) or all-cause mortality (RR, 0.98 [CI, 0.84 to 1.15]; RD, −4 [CI, −17 to 10]). Intensive glucose control increased the risk for severe hypoglycemia (RR, 2.03 [CI, 1.46 to 2.81]; RD, 39 [CI, 7 to 71]). As was seen in the overall analyses, pooled findings from the early and more recent trials showed that intensive glucose control reduced the risk for cardiovascular disease and increased the risk for severe hypoglycemia.

Limitation: Summary rather than individual data were pooled across trials.

Conclusion: Intensive glucose control reduced the risk for some cardiovascular disease outcomes (such as nonfatal myocardial infarction), did not reduce the risk for cardiovascular death or all-cause mortality, and increased the risk for severe hypoglycemia.

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The prevalence of type 2 diabetes is increasing globally (1–3). Epidemiologic evidence indicates that diabetes is a major risk factor for cardiovascular disease (CVD), and recent data suggest that the CVD burden attributable to diabetes is on the rise (4–7). Clinical trials have shown that intensive glucose control reduces the risk for microvascular complications among patients with type 2 diabetes, but its effect on CVD, including coronary heart disease (CHD), stroke, and peripheral arterial disease, is uncertain (8–10). Early data from the UKPDS (United Kingdom Prospective Diabetes Study) 34 suggested a protective effect of improved glucose control on CVD, CVD deaths, and all-cause mortality (11). However, within the past year, 3 large randomized, controlled trials have reported conflicting results (12–14). Although ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial) found no effect of intensive glucose control on major cardiovascular events (13, 14), ACCORD (Action to Control Cardiovascular Disease in Diabetes) identified an increased risk for death from cardiovascular causes and total mortality associated with intensive glucose control (12). On the basis of these results, a recent article by Montori and colleagues suggested that additional research is needed to confirm or refute the importance of tight glucose control (15). Thus, recommendations for health care providers regarding optimal hemoglobin A_{1c} (HbA_{1c}) levels in patients with type 2 diabetes remain unclear.

Because of the early termination of ACCORD and fewer events than anticipated in ADVANCE and VADT, there is real concern that these studies were underpowered to capture the true effects of intensive glucose control on CVD risk (12–14). Therefore, we conducted a meta-analysis of randomized, controlled trials to examine the effects of intensive glucose control on CVD among patients with type 2 diabetes. Furthermore, we examined the separate effects of intensive glucose control on all-cause mortality, CVD mortality, CHD, congestive heart failure (CHF), stroke, and peripheral artery disease. In an effort to explain incongruities among trial results, we conducted subgroup analyses and examined the occurrence of severe hypoglycemia.

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METHODS

Data Sources and Searches

We developed and followed a standard protocol for all steps of the review. Investigators searched the MEDLINE

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database (January 1950 through April 2009) using the Medical Subject Headings *cardiovascular diseases*; *coronary disease*; *stroke*; *peripheral vascular diseases*; *hypoglycemic agents*; and *diabetes mellitus, type 2*, as well as the keywords *coronary heart disease*, *glucose control*, and *glycemic control*. We restricted the search to randomized, controlled trials conducted among human adults (age ≥19 years), with no language restrictions. We also manually searched references cited in the published original reports and contacted experts in the field.

Study Selection

Two investigators independently reviewed the contents of 341 abstracts or full-text manuscripts identified through the literature search to determine whether they met the eligibility criteria. Studies were eligible for inclusion if 1) the study was a randomized, controlled trial; 2) the study compared intensive glucose control with conventional treatment, with a priori specification of glycemic goals for the intensive and conventional glucose control groups; 3) clinical CVD was the primary end point; 4) the study sample size was 500 patients or more; and 5) the study participants had type 2 diabetes mellitus. Reviewers resolved disagreements about study inclusion or exclusion by consensus and by referring to the original reports.

Data Extraction and Quality Assessment

Study investigators independently abstracted data in duplicate using a standardized data collection form. Reviewers did not contact authors to request additional information. Reviewers abstracted characteristics of each trial and its participants. Reviewers critically appraised methodological characteristics of trials, such as randomization procedures, blinded assessment of outcomes, adjudication procedures for outcomes, and follow-up rates, but did not use a scoring system to formally rate study quality of the individual trials (**Appendix Table 1**, available at www.annals.org).

Reviewers recorded the following as the main outcomes of interest: number of clinical CVD, CHD, stroke, and CHF events, along with cardiovascular deaths and all-cause mortality, for the intensive and conventional glucose control groups. Reviewers also recorded single end points, including nonfatal myocardial infarction, fatal myocardial infarction, nonfatal stroke, fatal stroke, and peripheral artery disease. In addition, reviewers recorded the number of severe hypoglycemic events for each trial group. Because definitions of certain composite outcomes varied between trials, each outcome is defined for each trial in **Appendix Table 2** (available at www.annals.org).

Data Synthesis and Analysis

We examined the relationship between intensive glucose control and risk for all study outcomes using relative risk and risk difference measures. We calculated the relative risks in each trial on the basis of the number of events in the intensive glucose control and conventional treatment groups and used these estimates for pooling analyses. To estimate the risk difference, we first calculated the annual absolute risk for an event in participants in each trial group by dividing the number of events in each trial group by the corresponding number of person-years (estimated as median treatment time × number of participants in the trial group). We then multiplied the annual absolute risk by 5 to estimate the 5-year risk among participants in each trial group. We calculated the risk difference for each trial by subtracting the 5-year risk in the conventional glucose control group from the 5-year risk in the intensive glucose control group. We logarithmically transformed the relative risks and risk differences and their corresponding standard errors to stabilize the variance and normalize their distribution. We pooled relative risks and risk differences using both fixed-effects and DerSimonian and Laird random-effects models (16). We used inverse variance weighting to calculate fixed- and random-effects summary estimates. We assessed heterogeneity formally by using the Dersimonian and Laird Q test, considering any P value less than 0.100 as evidence of heterogeneity, and by examining the I^2 quantity. Although fixed- and random-effects models yielded similar findings, we detected between-study heterogeneity for several study outcomes (severe hypoglycemia, cardiovascular deaths, all-cause mortality, and fatal myocardial infarction). Because of this heterogeneity and trial differences in median diabetes duration of participants, achieved HbA_{1c} levels, and therapeutic regimens, we present results from the random-effects models.

We conducted a prestated subgroup analysis to examine the effects of intensive glucose control on all study outcomes. We then compared the relative risks for CVD, CHD, CHF, stroke, cardiovascular deaths, all-cause mor-

Context

The relative benefits and harms of intensive versus conventional glucose control for type 2 diabetes are controversial.

Contribution

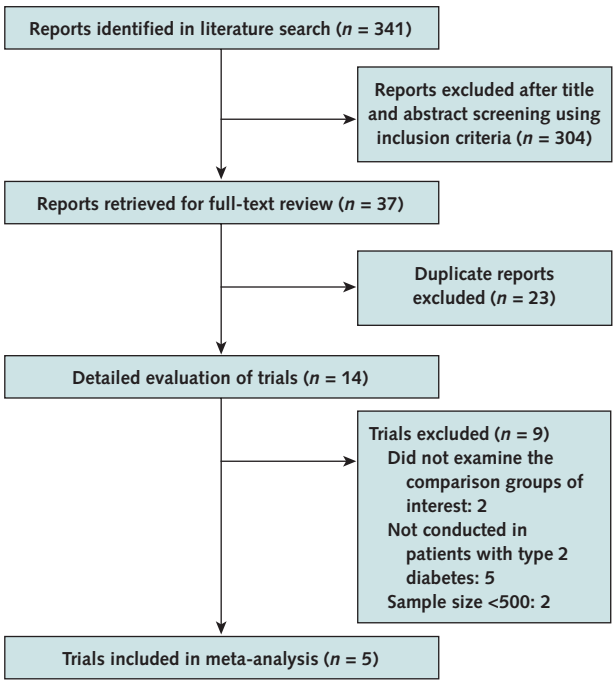
This review of 5 large trials found that, compared with conventional control, intensive glucose control reduced the risk for cardiovascular disease (mostly nonfatal myocardial infarction) but not for cardiovascular death or all-cause mortality, and increased risk for severe hypoglycemia. Trial design, achieved control, and findings were heterogeneous: Early trials suggested possible decreased risk for death with intensive control, whereas some more recent trials suggested possible increased risk for death with more stringent control.

Caution

The investigators did not evaluate costs. They pooled summary findings from trials rather than individual data from patients.

—The Editors

Figure 1. **Literature search and selection.**



tality, and severe hypoglycemia, as well as fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and peripheral artery disease between the early UKPDS trials (8, 11) and the 3 more recent ACCORD, ADVANCE, and VADT trials (12–14). We conducted all analyses by using Stata software, version 9.2 (Stata Corp, College Station, Texas).

Role of the Funding Source

This study was funded in part by a career development award from the National Heart, Lung, and Blood Institute and by an award from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The funding sources played no role in the study design; collection, analysis, and interpretation of the data; writing of the report; or decision to submit the paper for publication.

RESULTS

Figure 1 depicts the study selection process. We excluded 2 trials, the Kumamoto Study (n = 110) and the Veterans Affairs (VA) Diabetes Feasibility Trial (n = 153), because of small sample sizes (9, 17). The VA Diabetes Feasibility Trial was a pilot study that examined whether intensive glucose control could be effectively sustained in patients with type 2 diabetes and was a precursor to the subsequent VADT. The Kumamoto Study examined the effects of intensive glucose control on microvascular complications of diabetes. The current meta-analysis included a total of 5 trials conducted among 27 802 participants (8, 11–14). **Table 1** presents the characteristics of the 5 randomized, controlled trials and trial participants. The number of trial participants ranged from 753 to 11 140, while intervention duration ranged from 3.4 to 10.7 years. The UKPDS 33 and 34 recruited participants with newly diagnosed diabetes. Those inclusion criteria differed from those of ADVANCE, ACCORD and VADT, whose participants had an average duration of diabetes ranging from 7.9 to 11.5 years at the time of trial enrollment. Although the VADT did not provide data on aspirin use, that therapy seemed to be more common in recent trials than in the earlier UKPDS 33 and 34.

Table 2 shows the average pre- and postintervention values of key CVD risk factors in trial participants. On average, trial participants were overweight, with mean baseline body mass index ranging from 28 to 32 kg/m^2. Postintervention weight in ACCORD, ADVANCE, and VADT was higher among patients in the intensive groups than those in the conventional groups. Systolic blood pressure seemed to decrease between the preintervention and posttrial period in ACCORD, ADVANCE, and VADT, whereas average diastolic blood pressure decreased in all studies. In general, average high-density lipoprotein cholesterol levels did not change from baseline to the end of the study, whereas both low-density lipoprotein cholesterol and triglyceride levels decreased in participants of all trials. The HbA_{1c} values decreased from before to after the intervention in ACCORD, ADVANCE, and VADT and increased over the trial periods of the UKPDS 33 and 34. Postintervention HbA_{1c} levels in the intensive groups of the UKPDS 33 and 34 were higher than those in the conventional groups of ACCORD, ADVANCE, and VADT. All trials showed lower postintervention HbA_{1c} levels in the intensive than in the conventional glucose control group, with median differences ranging from −0.5% to −1.4%. The sample size–weighted overall difference in median HbA_{1c} levels was −0.8%.

Figure 2 presents the individual and pooled relative risks and risk differences (per 1000 patients over 5 years of treatment) of CVD, CHD, stroke, CHF, cardiovascular deaths, and all-cause mortality for the 5 trials. Overall analyses indicated that patients randomly assigned to intensive glucose control had reduced risk for CVD (relative risk, 0.90 [95% CI, 0.83 to 0.98]; risk difference, −15 [CI, −24 to −5]) and CHD (relative risk, 0.89 [CI, 0.81 to 0.96]; risk difference, −11 [CI, −17 to −5]) compared with participants in the conventional treatment groups, with similar findings from subgroup analyses of the early UKPDS and more recent ACCORD, ADVANCE, and VADT. We observed no overall effect of intensive glucose control on cardiovascular mortality (relative risk, 0.97 [CI, 0.76 to 1.24]; risk difference, −3 [CI, −14 to 7]) or all-cause mortality (relative risk, 0.98 [CI, 0.84 to 1.15]; risk difference, −4 [CI, −17 to 10]), but we identified possible heterogeneity between the results of subgroup analyses (P for heterogeneity between subgroups = 0.095 and 0.105,

Table 1. **Characteristics of 5 Randomized, Controlled Trials of Intensive Glucose Control**

Characteristic	UKPDS 33, 1998 (8)	UKPDS 34, 1998 (11)	ACCORD, 2008 (12)	ADVANCE, 2008 (13)	VADT, 2009 (14)
Participants, *n*	3867	753	10 251	11 140	1791
Median duration of intervention, *y*	10.0	10.7	3.4	5.0	5.6
Treatment					
Intensive glucose control	Sulfonylurea or insulin	Metformin	≥2 classes of hypoglycemic agents plus other drugs	Gliclazide plus other drugs	Glimepiride or metformin, plus rosiglitazone, or insulin
Conventional glucose control	Diet	Diet	Diet or pharmacologic treatment, or both	Continue current therapy, if necessary; patients taking gliclazide substituted the drug with another sulfonylurea	Glimepiride or metformin, plus rosiglitazone, or insulin
Treatment goal					
Intensive glucose control	FPG level <6.0 mmol/L (<108 mg/dL)	FPG level <6.0 mmol/L (<108 mg/dL)	HbA_{1c} level <6.0%	HbA_{1c} level ≤6.5%	HbA_{1c} level <6% and 1.5% less than conventional
Conventional glucose control	FPG level, 6.1–15.0 mmol/L (110–270 mg/L)	FPG level, 6.1–15.0 mmol/L (110–270 mg/L)	HbA_{1c} level, 7.0%–7.9%	Local standards	HbA_{1c} level <9% and 1.5% higher than intensive
Mean age, *y*	53.3	53.0	62.2	66.0	60.4
Men, %	61	47	61	58	97
Race/ethnicity, %					
White	81	86	64	NR	62
Asian	10	5	NR	NR	NR
Black	8	8	19	NR	17
Hispanic	NR	NR	7	NR	16
Other	1	1	NR	NR	5
Mean duration of diabetes, *y*	0.0*	0.0*	10.0†	7.9	11.5
Aspirin use, %	2	2	55	44	NR
History of cardiovascular disease, %	NR	NR	35	32	40

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; NR = not reported; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
* The UKPDS 33 and 34 trials recruited participants with newly diagnosed diabetes.
† Median.

respectively). Pooled findings from the early UKPDS trials showed non–statistically significant protective effects of intensive glucose control on cardiovascular and all-cause mortality. In contrast, summary data from ACCORD, ADVANCE, and VADT indicated non–statistically significant increased risks for these outcomes in the intensive glucose control group. There were no reductions in the overall risk for stroke or CHF associated with intensive glucose control.

Figure 3 shows the pooled relative risks and risk differences of nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and peripheral artery disease in the early and more recent trial subgroups and overall. ACCORD did not present results on peripheral artery disease, and pooled findings for this outcome represent the combined results of the 4 other trials. After pooling the relative risks across all 5 trials, we observed a 20% reduced risk for nonfatal myocardial infarction associated with intensive glucose control in the UKPDS trials; 15% in ACCORD, ADVANCE, and VADT; and 16% overall. We observed absolute risk reductions of 9 events per 1000 patients over 5 years of treatment in the overall and subgroup analyses. In contrast, we observed no associations between intensive glucose control and fatal myocardial infarction, nonfatal stroke, fatal stroke, or peripheral artery disease in subgroup or overall analyses.

Figure 4 shows the occurrence of severe hypoglycemia. Intensive glucose control was associated with a 2-fold increase (absolute increase of 39 events per 1000 patients over 5 years) in severe hypoglycemia in the overall analysis, with no association in the early UKPDS studies, and a 2.5-fold increase (absolute increase of 54 events per 1000 patients over 5 years) in the more recent trials.

We conducted a sensitivity analysis to determine whether the 2 studies that were excluded because of small sample size would have changed the results of the current analysis (9, 17). Inclusion of these studies did not alter any of the main findings, with nearly identical relative risks of 0.91 (CI, 0.82 to 1.00) for CVD, 0.89 (CI, 0.82 to 0.96) for CHD, 0.98 (CI, 0.85 to 1.13) for stroke, 1.01 (CI, 0.88 to 1.16) for CHF, 0.96 (CI, 0.76 to 1.21) for cardio-

Table 2. **Risk Factors for Cardiovascular Disease in Trial Participants Before and After the Intervention**

Risk Factor	UKPDS 33, 1998 (8)		UKPDS 34, 1998 (11)		ACCORD, 2008 (12)	
	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control
Mean weight, *kg*						
Before intervention	78.1	77.3	87.0	87.0	93.6	93.5
After intervention	79.0†	80.0†	87.0†	86.0†	94.0‡	97.0‡
Mean body mass index, *kg/m²*						
Before intervention	28	28	32	32	32	32
After intervention	29	29	32	32	NR	NR
Mean blood pressure, *mm Hg*						
Systolic						
Before intervention	135	135	140	140	137	136
After intervention	138	139	139	141	127	126
Diastolic						
Before intervention	82	83	86	85	75	75
After intervention	77	77	77	78	68	67
Lipid levels, *mmol/L (mg/dL)*						
Median triglyceride						
Before intervention	2.31 (204§)‖	2.37 (210§)‖	2.96 (262§)‖	2.79 (247§)‖	1.74§ (154)	1.76§ (156)
After intervention	1.45§ (128)	1.45§ (127)	1.62§ (143)	1.77§ (157)	NR	NR
Mean HDL cholesterol						
Before intervention	1.08 (42¶)	1.07 (41¶)	1.04 (40¶)	1.06 (41¶)	1.09¶ (42)	1.09¶ (42)
After intervention	1.11¶ (43)	1.09¶ (42)	1.04¶ (40)	1.11¶ (42)	NR	NR
Mean LDL cholesterol						
Before intervention	3.5 (135¶)	3.5 (135¶)	3.66 (141¶)	3.67 (142¶)	2.72¶ (105)	2.72¶ (105)
After intervention	3.26¶ (126)	3.26¶ (126)	3.34¶ (129)	3.37¶ (130)	2.36¶ (91)	2.36¶ (91)
Median hemoglobin A_{1c} level, %						
Before intervention	6.9**	7.0**	7.0**	7.0**	8.1	8.1
After intervention	8.5	7.9	8.9	8.4	7.2	6.2

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
* Estimated on the basis of reported weight in pounds by using a conversion factor of 0.45.
† Median.
‡ Calculated on the basis of net change in weight over the study period.
§ Estimated by multiplying (dividing) by a conversion factor of 0.0113.
‖ Geometric mean.
¶ Estimated by multiplying (dividing) by a conversion factor of 0.0259.
** Estimated from figure.
†† Mean.

vascular deaths, and 0.98 (CI, 0.85 to 1.14) for total deaths.

DISCUSSION

Combining data from nearly 28 000 participants of 5 large randomized, controlled trials, the current study documented that intensive glucose control was associated with a 10% reduction in the risk for CVD and an 11% reduction in the risk for CHD, with corresponding absolute risk reductions of 15 and 11 events per 1000 patients over 5 years of treatment. Subgroup analyses of the early UKPDS trials and the more recent ACCORD, ADVANCE, and VADT had similar findings. In addition, intensive glucose control decreased the risk for nonfatal myocardial infarction by 16%, or an absolute reduction of 9 events per 1000 patients over 5 years of treatment. This association persisted in subgroup analyses, with risk reductions of 20% (absolute reduction, 9 events per 1000 patients over 5 years of treatment) in the UKPDS trials and 15% (absolute reduction, 9 events per 1000 patients over 5 years of treatment) in ACCORD, ADVANCE, and VADT. The protective effect of intensive glucose control on nonfatal myocardial infarction is probably the driving force behind the observed decreases in overall CVD and CHD risk. We observed no overall effect of intensive glucose control on cardiovascular or all-cause mortality. However, the early UKPDS trials suggested that intensive glucose control might reduce mortality from CVD and all causes. In contrast, some of the more recent trials suggested that more stringent glucose control might increase mortality from CVD and all causes. In addition, we observed a 2-fold increased risk for severe hypoglycemia (39 excess

Table 2—**Continued**

ADVANCE, 2008 (13)		VADT, 2009 (14)	
Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control
78.0	78.2	96.3*	96.3*
77.0	78.1	100.4*	104.4*
28	28	31	31
28	28	32	34
145	145	132	131
138	136	125	127
81	81	76	76
74	74	69	68
1.64 (145§)	1.60 (142§)	2.52§ (223)	2.27§ (201)
1.59 (141§)	1.45 (128§)	1.80§ (159)	1.71§ (151)
1.25 (48¶)	1.26 (49¶)	0.93¶ (36)	0.93¶ (36)
1.25 (48¶)	1.24 (48¶)	1.06¶ (41)	1.04¶ (40)
3.11 (120¶)	3.12 (121¶)	2.80¶ (108)	2.77¶ (107)
2.65 (102¶)	2.64 (102¶)	2.07¶ (80)	2.07¶ (80)
7.2	7.2	9.4††	9.4††
7.0	6.3	8.5	7.1

events per 1000 patients over 5 years of treatment) associated with intensive glucose control. Our study does not support associations between intensive glucose control and reduced risks for CHF, fatal myocardial infarction, fatal and nonfatal stroke, and peripheral artery disease.

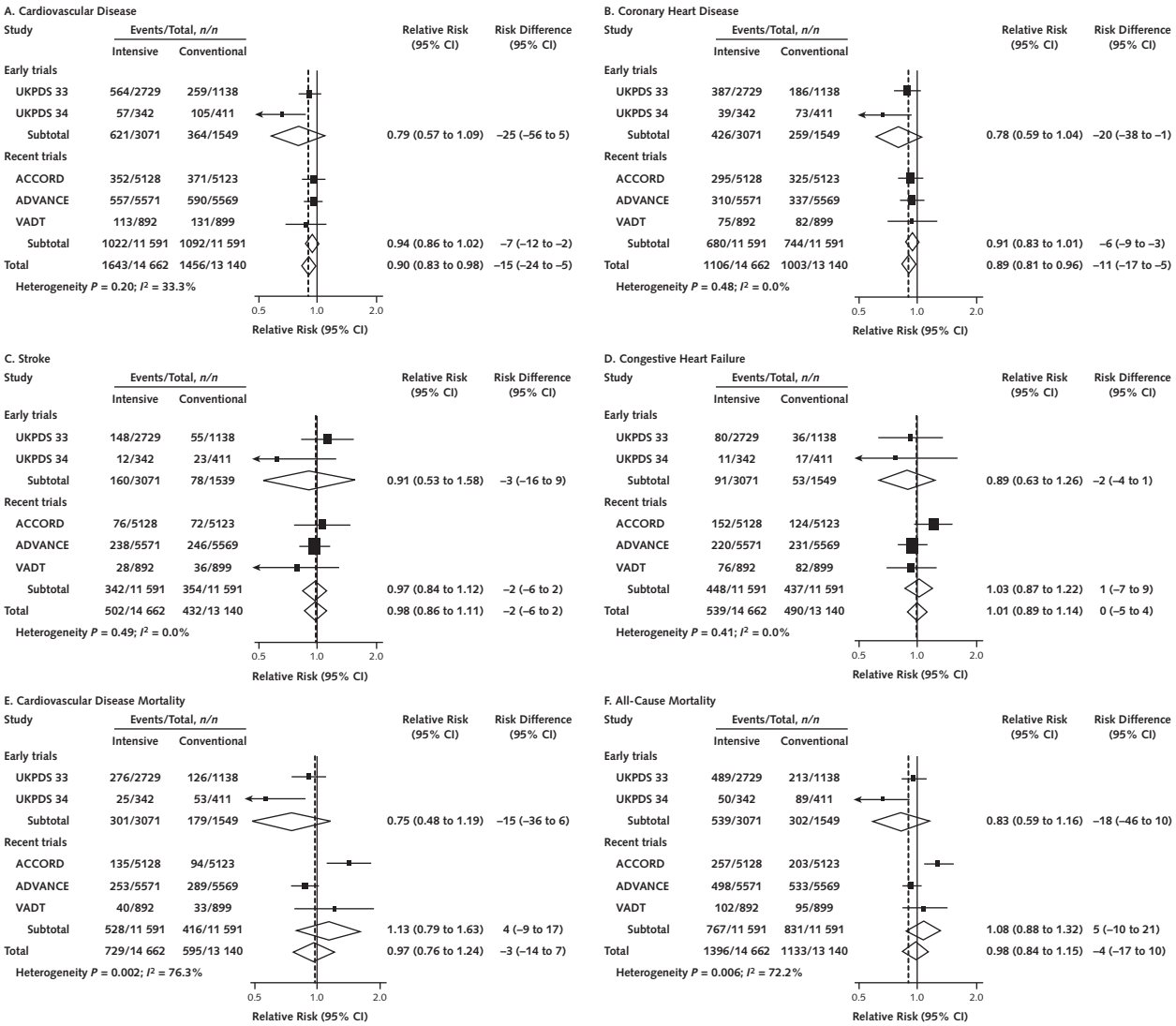
Important differences in therapeutic regimens and achieved HbA_{1c} levels existed among the 5 trials included in our meta-analysis. Each trial used different combinations of diet, sulfonylureas, thiazolidinediones, metformin, or insulin therapies to achieve target levels of glucose control. The UKPDS 33 and 34 limited participant recruitment to patients with newly diagnosed diabetes and used diet as the primary method of treatment in the conventional glucose control group. In contrast, the more recent ACCORD, ADVANCE, and VADT studies, which recruited participants with diabetes of much longer duration, relied primarily on pharmacologic therapy in the conventional control group. In addition, differences in achieved HbA_{1c} levels between the studies were substantial. We observed smaller differences in median HbA_{1c} levels between the intensive and conventional glucose control groups in the UKPDS 33 and 34 compared with the more recent trials. Furthermore, the UKPDS 33 and 34 attained postintervention median HbA_{1c} levels in the intensive treatment group that were similar to or higher than those achieved in the conventional treatment groups of ACCORD, ADVANCE, and VADT. By today's standards, the UKPDS 33 and 34 examined the benefits of conventional pharmacologic treatment, initially and predominantly as monotherapy, whereas the later 3 trials investigated what is generally accepted as intensive glucose control. Because of these substantial differences, we examined the UKPDS trials separately from ACCORD, ADVANCE, and VADT in subgroup analyses. Of note, we consider these results in the interpretation of the data.

We observed protective effects of intensive glucose control on the risk for CVD, CHD, and nonfatal myocardial infarction in the overall analysis, with similar trends supported in our subgroup examinations. Similar to our findings, a 2006 meta-analysis of randomized, controlled trials by Stettler and colleagues identified an association between intensive glucose control and both cardiac events and any macrovascular event among patients with type 1 or type 2 diabetes (18). Although we did not identify effects of intensive glucose control on other CVD end points, Stettler and colleagues found associations between intensive glucose control and peripheral artery disease and cerebrovascular disease (18).

Several differences between the 2 meta-analyses could explain the conflicting findings. The 2006 meta-analysis was conducted before the release of ACCORD, ADVANCE, and VADT findings and represent results from the UKPDS studies, as well as the VA Diabetes Feasibility Trial and Kumamoto Study, which were not powered to examine CVD end points (9, 17, 18). Inclusion of these 2 trials in a sensitivity analysis did not change our results. Moreover, methodological weaknesses, including the use of fixed-effects models to pool potentially heterogeneous studies, were evident. Our findings also contrast with those of observational studies, which have identified consistent, positive associations between HbA_{1c} and peripheral artery disease, CHF, fatal CHD, and stroke among patients with type 2 diabetes (19–21). Several explanations for these discrepancies exist. Of note, results from observational studies are subject to confounding effects of unknown or poorly measured risk factors. It is possible that the observational designs did not adequately control for such variables as healthy lifestyle and access to health care, which are associated with glucose control. Furthermore, clinical trials are typically shorter than prospective observational studies, a difference that could contribute to discrepancies in their results.

The premature termination of ACCORD due to excess mortality in the trial's intensive treatment group alarmed both clinicians and investigators alike (12, 22). Although summary findings of the current meta-analysis do not support these results, analyses of some of the more recent trials suggested that intensive glucose control might increase risks for cardiovascular and all-cause mortality,

Figure 2. **Pooled relative risk and risk difference (per 1000 patients over 5 years of treatment) estimates, with 95% CIs, for main study outcomes, by trial, early and more recent trial subgroups, and overall.**



ACCORD = Action to Control Cardiovascular Risk in Diabetes (12); ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (13); UKPDS = United Kingdom Prospective Diabetes Study (8, 11); VADT = Veterans Affairs Diabetes Trial (14).

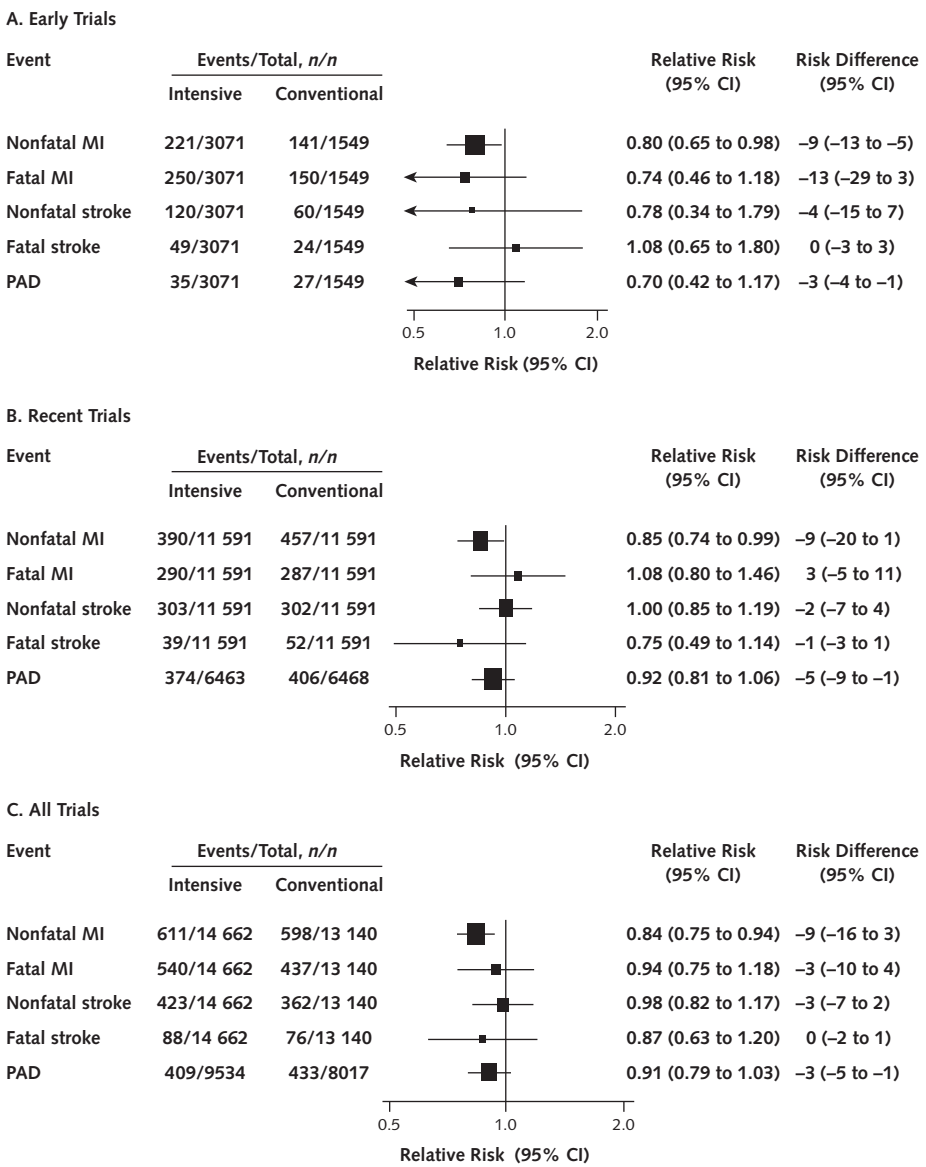
which is in part due to the contribution of findings from ACCORD. In ACCORD, much of the excess mortality in the intensive glucose control group was due to cardiovascular causes, particularly fatal myocardial infarction, CHF, and "unexpected or presumed CVD." The use of the thiazolidinedione rosiglitazone has been linked to an increased risk for myocardial infarction and is known to precipitate CHF in susceptible patients (23, 24). This antihyperglycemic agent was more commonly used in the intensive than in the conventional treatment group (91.2% vs. 57.5%) of ACCORD and may explain some of the observed increases in myocardial infarction and CHF deaths (12). In contrast, thiazolidinediones were not used in the UKPDS trials and were used similarly in the intensive and conventional groups of ADVANCE and VADT (although higher maximum doses were used in the intensive treatment group of VADT). In addition, it has been suggested that excess mortality in ACCORD resulted from deaths due to severe hypoglycemia (22). It may be important to explore whether deaths from severe hypoglycemia could have been incorrectly ascertained in this trial as "unexpected or presumed CVD" deaths.

We identified severe hypoglycemia as an adverse effect strongly associated with intensive glucose control in the present study. Subgroup results from ACCORD, ADVANCE, and VADT found a particularly pronounced treatment ef-

fect, with a 2.5-fold increased risk for hypoglycemia, or an absolute increase of 54 events per 1000 patients over 5 years of treatment, associated with intensive glucose control. ACCORD showed the largest relative risk for hypoglycemia, followed closely by VADT. As with ACCORD, VADT had an increased number of sudden deaths in the intensive compared with the conventional glucose control groups, again calling attention to the possibility of incorrect ascertainment of hypoglycemia-related deaths. Secondary analyses examining the effect of lower HbA_{1c} thresholds on mortality could provide important information on this topic.

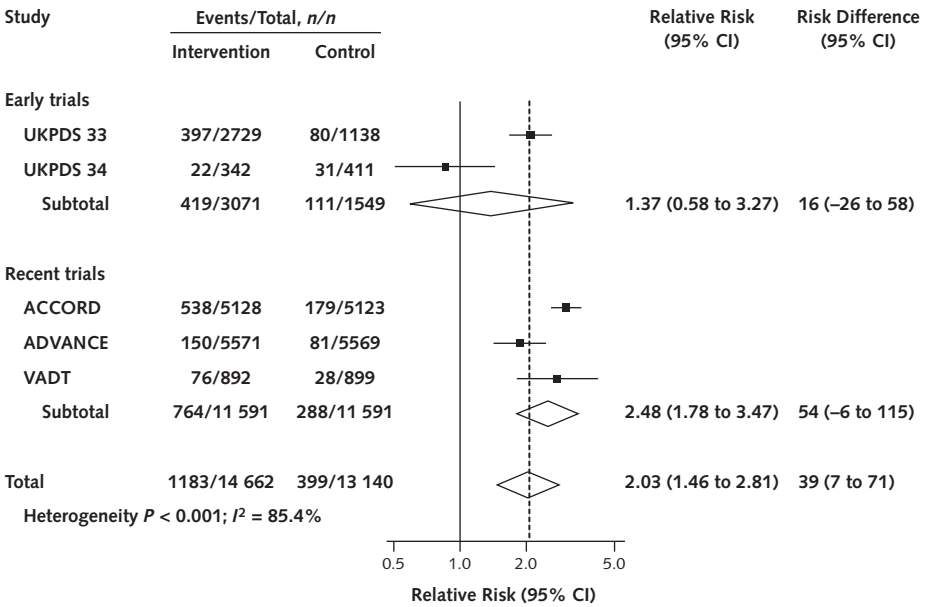
With more than 27 000 participants among the 5 trials, we had excellent power to detect small but clinically important effects of intensive glucose control on major cardiovascular end points and all-cause mortality. In contrast, the power of subgroup analyses to detect small effects of intensive glucose control was limited. A further limitation of the current study includes the use of summary data rather than individual-patient data from the 5 included trials. In addition, the recent clinical trials of intensive therapy were of relatively shorter duration than the UKPDS and raise the issue of inadequate time for demonstration of some cardiovascular and total mortality benefits.

Figure 3. **Pooled relative risk and risk difference (per 1000 patients over 5 years of treatment) estimates of nonfatal MI, fatal MI, nonfatal stroke, fatal stroke, and PAD.**



MI = myocardial infarction; PAD = peripheral artery disease.

Figure 4. **Pooled relative risk and risk difference (per 1000 patients over 5 years of treatment) estimates of severe hypoglycemia, by trial, early and more recent trial subgroups, and overall.**



ACCORD = Action to Control Cardiovascular Risk in Diabetes (12); ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (13); UKPDS = United Kingdom Prospective Diabetes Study (8, 11); VADT = Veterans Affairs Diabetes Trial (14).

ACCORD stopped intensive treatment after 3.5 years rather than the planned 5 years, and it may be unrealistic to expect a significant reduction in events over this relatively short time frame. This issue is relevant in light of the finding that myocardial infarction and mortality were reduced on long-term follow-up of the UKPDS intensive therapy cohort (10, 11).

The results of this meta-analysis provide some evidence for a beneficial effect of intensive glucose control on CVD, particularly on nonfatal myocardial infarction, but not on cardiovascular deaths and all-cause mortality in patients with type 2 diabetes. Similar to the current study, a recent meta-analysis by Ray and colleagues identified a protective effect of intensive glucose control on CHD and nonfatal myocardial infarction, with no overall effect of intensive glucose control on stroke or all-cause mortality (25). Moreover, they identified important trial heterogeneity in all-cause mortality findings. We explored this inconsistency with subgroup analyses and add findings that suggest decreased risks for both cardiovascular and all-cause mortality in early trials, compared with possible increased risks in the more recent trials that used more stringent intensive glucose control. Furthermore, our results emphasize severe hypoglycemia as an important adverse effect of intensive glucose control. In light of these findings, it is important to consider how best to approach the prevention of CVD and death in this high-risk population. Randomized trials have consistently shown that interventions for lipid-lowering and blood pressure reduction are extremely effective in decreasing CVD and all-cause mortality among patients with type 2 diabetes (26–29). Multifactorial interventions combining glucose regulation, blood pressure control, aspirin use, and lipid-lowering agents have been shown to decrease cardiovascular events by 59%, cardiovascular deaths by 57%, and total deaths by 46% in a type 2 diabetes population (30, 31). Nevertheless, there remains a residual excess risk among diabetic patients after adjustment for blood pressure and lipids (6, 32, 33). Additional approaches are needed to reduce this risk, ones that do not increase risks for severe hypoglycemia and weight gain, as observed in some of the trials examined here. The recent BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) conducted among patients with type 2 diabetes and CHD indicated that insulin sensitization compared with insulin provision resulted in fewer severe hypoglycemic episodes, less weight gain, greater high-density lipoprotein cholesterol levels, and better glucose control among these patients (34). Because BARI 2D was not designed to distinguish between the effects of insulin-sensitization agents, such as thiazolidinediones and metformin, more research in this area will be needed. Until then, health care providers should focus their efforts on combining elements of lifestyle modification, glucose control that minimizes hypoglycemia, blood pressure reduction, and lipid lowering to optimally curtail the risk for CVD in patients with type 2 diabetes.

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Appendix Table 1. **Assessment of Methodological Characteristics**

Study, Year (Reference)	Study Design	Randomization Procedures	Blind Assessment of Outcomes	Adjudication Procedures for Outcomes	Intention-to-Treat Analysis	Follow-up Rates, %
UKPDS 33, 1998 (8)	Randomized, open-label design	Centrally produced, computer-generated allocation in sealed, opaque envelopes opened in sequence	Yes	Discussion and review of the evidence by 2 independent physicians. If agreement was not possible, the file was submitted to 2 different assessors for final arbitration.	Yes	95.7
UKPDS 34, 1998 (11)	Randomized, open-label design	Centrally produced, computer-generated allocation in sealed, opaque envelopes opened in sequence	Yes	Discussion and review of the evidence by 2 independent physicians. If agreement was not possible, the file was submitted to 2 different assessors for final arbitration.	Yes	92.6
ACCORD, 2008 (12)	Randomized, double 2 × 2 factorial, open-label design	NA	Yes	Outcomes were adjudicated by a central committee unaware of study group assignment.	Yes	97.8
ADVANCE, 2008 (13)	Randomized, 2 × 2 factorial, open-label design	Central, computer-based randomization	Yes	An independent end point adjudication committee, unaware of group assignments, reviewed source documentation for all suspected primary end points and deaths.	Yes	99.8
VADT, 2009 (14)	Randomized, permuted-block, open-label design	Randomization codes were generated by the study's biostatistician at the Hines Cooperative Studies Program Coordinating Centers	Yes	Outcomes were adjudicated by an end point committee that was unaware of study group assignments.	Yes	85.5

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Appendix Table 2. **Definitions of Composite Outcomes for Each Trial**

Composite End Point	UKPDS 33, 1998 (8)	UKPDS 34, 1998 (11)	ACCORD, 2008 (12)	ADVANCE, 2008 (13)	VADT, 2009 (14)
Cardiovascular disease	Fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and amputation and death from peripheral artery disease	Fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and amputation and death from peripheral artery disease	Nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, death from heart failure, arrhythmia, invasive cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, and other vascular diseases (e.g., pulmonary emboli, abdominal aortic aneurysm rupture)	Nonfatal myocardial infarction and stroke and cardiovascular death	Nonfatal myocardial infarction and stroke, death from myocardial infarction, stroke, heart failure, coronary revascularization, stroke, cerebrovascularization, complications from occlusions, peripheral revascularization, sudden death, and pulmonary embolism
Coronary heart disease	Fatal and nonfatal myocardial infarction and sudden death	Fatal and nonfatal myocardial infarction and sudden death	Nonfatal and fatal myocardial infarction, unexpected or presumed cardiovascular death, and fatal arrhythmia	Nonfatal myocardial infarction, sudden death, and death from coronary heart disease	Fatal and nonfatal myocardial infarction and sudden death
Stroke	Fatal and nonfatal stroke	Fatal and nonfatal stroke	Fatal and nonfatal stroke	Nonfatal stroke and death due to cerebrovascular disease	Fatal and nonfatal stroke
Congestive heart failure	Fatal and nonfatal congestive heart failure	Fatal and nonfatal congestive heart failure	Fatal and nonfatal congestive heart failure	Hospitalization or death due to heart failure or worsening of New York Heart Association class	Fatal and nonfatal congestive heart failure
Cardiovascular deaths	Death from myocardial infarction, stroke, sudden death, or peripheral artery disease	Death from myocardial infarction, stroke, sudden death, or peripheral artery disease	Death from myocardial infarction, stroke, heart failure, arrhythmia, invasive cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, and other vascular diseases (e.g., pulmonary emboli, rupture of abdominal aortic aneurysm)	Death from cardiovascular causes	Death from myocardial infarction, stroke, heart failure, coronary revascularization, cerebrovascularization, complications from occlusions, peripheral revascularization, sudden death, and pulmonary embolism
Peripheral artery disease	Amputation or death from peripheral artery disease	Amputation or death from peripheral artery disease	NA	Peripheral vascular events	Amputation and fatal and nonfatal peripheral revascularization
Severe hypoglycemia	Hypoglycemic event requiring medical or third-party intervention	Hypoglycemic event requiring medical or third-party intervention	Hypoglycemia requiring medical assistance	Hypoglycemia that caused transient dysfunction of the central nervous system and prevented patients from treating themselves	Hypoglycemia that was life-threatening or fatal, caused disability or incapacity, or required hospitalization or medical intervention

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