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Update in Diabetes and CVD: Synthesizing the Evidence from Recent Trials of Glycemic Control to Prevent Cardiovascular Disease

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Abstract

Purpose of review—To review the recent studies on intensive glucose control and the risk of cardiovascular disease (CVD) in type 2 diabetes, to discuss potential reasons for discordant results among recent trials, and to comment on implications for clinical practice.

Recent findings—Three large randomized controlled trials on the effect of tight glycemic control (TGC) on CVD in patients with type 2 diabetes have been published within the last year, along with the cardiovascular outcomes from the long-term follow-up of the UKPDS study. This narrative review of the methods and results of these trials reveals cardiovascular benefit from early institution of TGC, and lack of benefit or potential harm with intensification of glucose control late in the course of type 2 diabetes or after CVD has developed. Also, the benefits of TGC may be outweighed by weight gain and hypoglycemia. All trials had fewer cardiovascular events than anticipated due to improvements in other cardiovascular risk factors.

Summary—In addition to controlling cardiovascular risk factors, patients with type diabetes should aim for good glycemic control (HbA1c<7%) soon after the diagnosis of diabetes to prevent macrovascular as well as microvascular complications. Glycemic targets should be individualized as diabetes progresses, comorbidities develop, and to avoid having the side effects of therapy (hypoglycemia and weight gain) predominate.

Keywords

Diabetes mellitus; cardiovascular disease; glucose control

Introduction

While diabetes and dysglycemia are associated with an increased risk of cardiovascular disease (CVD) [1–6], randomized controlled trial (RCT) evidence of the benefit of tight glycemic control (TGC) on cardiovascular (CV) outcomes has been elusive in subjects with type 2 diabetes [7,8]. In the past year, three RCTs [9**,10**,11**] examining the impact of TGC on CV outcomes have been published. Together with results from the seminal longitudinal studies

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in diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) [12–14**] and the Diabetes Control and Complications Trial (DCCT) [15**], findings range from reports that TGC decreases CVD risk to reports that TGC increases harm. The goal of this narrative review is to build on the quantitative findings of recent meta-analyses [16*,17*] to outline the differences among the studies in order to gain insight into application to different patient populations. Importantly, the benefit of TGC on preventing or delaying microvascular complications of diabetes is not in doubt [10**,11**,12,13,15**]. The totality of the evidence suggests that TGC may be most effective in preventing CV outcomes when instituted early in the disease course, and when the cost of the therapy (in terms of weight gain and hypoglycemia), does not predominate.

Summary of recent trials

The ACCORD study (Action to Control Cardiovascular Risk in Diabetes) randomly assigned 10,251 subjects with type 2 diabetes with median HbA1c 8.1% and a history of CVD or CVD risk factors to intensive therapy (goal HbA1c of <6%) versus conventional therapy (goal HbA1c of 7.0 to 7.9%) (see Table 1 for comparison with other trials). Patients in the intensive group were significantly more likely to require multi-drug regimens to achieve this goal, and were significantly more likely to be on thiazolidinediones (91.7% vs. 58.3%), nearly all other hypoglycemic agents, and combination regimens. This trial was stopped after an interim analysis at 3.5 years of follow up because of an increased risk of overall mortality (5.0% vs. 4.0%, $P=0.04$) and CVD death (2.6% vs. 1.8%, $P=0.02$) in the intervention group. In contrast, the study found a decrease in non-fatal MI (3.6% in the intervention group vs. 4.6% in the conventional group $P=0.004$) (see Table 2 for comparison with other trials) [9**].

The ADVANCE study studied 11,140 subjects with type 2 diabetes and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. The intensive glycemic control group used sulfonylurea (glicazide)-based therapy to achieve a HbA1c goal of $\leq 6.5\%$. After a median 5 years of follow-up, the study found a benefit to TGC in the composite outcome of microvascular and macrovascular events, with the benefit largely due to a decrease in the development of macroalbuminuria (2.9% vs. 4.1%, $P<0.001$). The study did not find a significant difference in macrovascular events between the groups (death from CVD 4.5% vs. 5.2%, nonfatal MI 2.7% vs. 2.8%, and death from any cause 8.9% vs. 9.6%) [10**].

The Veterans Administration Diabetes Trial (VADT) was conducted in 1,791 veterans with type 2 diabetes who had inadequate response to maximal doses of oral and/or daily insulin injections with HbA1c $\geq 7.5\%$, and targeted an absolute HbA1c reduction of 1.5% between the intervention and conventional groups. The study excluded those with Canadian Heart Association class III or IV angina pectoris and those with New York Heart Association class III or IV heart failure [18]. Over a median of 5.6 years of follow-up, the study found no overall difference in CV or macrovascular events between the two groups (death from CVD 4.5% vs. 3.7%, death from any cause 11.4% vs. 10.6%). There was a reduction in worsening of albumin excretion rate and progression to macroalbuminuria in the intensive group [11**].

While these trials were very large, duration of follow-up was nonetheless short relative to the duration of diabetes and expected time course of development of complications. As a counterpoint to these trials, we review the follow-up experience of the long-term diabetes RCTs.

The UKPDS study was started in 1977, with the original results published in 1998. The study enrolled a total of 4,620 patients newly diagnosed with type 2 diabetes into several arms, depending on body weight: starting with sulfonylurea, insulin, or metformin for TGC versus conventional treatment. The studies aimed for fasting plasma glucose of <6 mmol/L (108 mg/

dL) in the intensive groups, while the conventional groups were treated with diet unless symptoms developed or fasting plasma glucose exceeded 15 mmol/L (270 mg/dl) [12,13]. The sulfonylurea and insulin-based intervention group achieved a median HbA1c of 7.0%, compared to 7.9% in the conventional group, and the metformin-based group achieved HbA1c of 7.4%, compared to 8% [12,13]. The original studies found that any intensive glucose therapy lowered the risk of microvascular complications and any diabetes-related endpoint [12,13]. Specifically relevant to this review, the metformin group had an 11% rate of MI compared to an 18% rate in the conventional group ($P=0.01$) [12].

The long-term follow-up data on this cohort provides further information about glycemic control and CVD risk. During the 10 years after the original trial, subjects in all groups maintained a median HbA1c of 8.0% or higher. Nonetheless, significant differences in macrovascular events between groups emerged. In the sulfonylurea and insulin cohorts, the event rate of MI (including fatal MI) was lower in the intensive control group (24.8% vs. 28%) for a 15% risk reduction overall ($P=0.01$). There was also a 13% relative risk reduction of death from any cause between the groups (42.6% vs. 47.2%, $P=0.007$). In the metformin group, the risk reductions were even greater: the event rate for MI (including fatal MI) was lower in the intensive group (38.8% vs. 48% $P=0.005$) for a 33% relative risk reduction. There was also a 27% risk reduction in death from any cause between groups (44.4% vs. 52.8%, $P=0.002$) [14**].

While the prior trials focus on subjects with type 2 diabetes, it is instructive to compare these outcomes to those available from subjects with type 1 diabetes, who have absolute insulin deficiency. The DCCT followed 1,441 young (mean age 27) subjects with type 1 diabetes for 6.5 years, during which the intensive treatment group achieved a mean HbA1c of 7.4% and the conventional group achieved a mean HbA1c of 9.1% [19]. Subsequently patients were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) observational study, during which mean HbA1c was ~8% in both groups [15**]. Analysis of CV endpoints was undertaken when the pre-specified event frequency was achieved in 2005. The composite CV event outcome was lower in the intervention group compared to the conventional group: the event rates were 0.38 and 0.80 per 100 patient years ($P=0.007$) in the intensive and conventional groups respectively. The study also found that the intensive group had a 42% reduction in risk to first CVD event ($P=0.02$), and a 57% reduction in risk of first non-fatal MI, stroke or death ($P=0.02$) [15**].

Major differences between recent trials

It is not possible to explain with certainty why the trials reached such different conclusions, but examining differences between the trials may provide guidance and useful clinical insights (see Table 1).

Percentage of subjects with CVD

The VADT (at 40%) [11**] and ACCORD (at 35%) [9**] trials had the highest percent of patients with CVD at baseline. Only 12% of patients in ADVANCE had a history of previous MI (32% with MI, stroke, other) [10**] and the UKPDS trial excluded subjects with MI within the last year, more than one vascular event, and active angina or CHF [12,13]. DCCT excluded patients with CVD [15**].

Age and duration of diabetes

DCCT was a study of type 1 diabetes with average age of 27 and disease duration of an average of 5.5 years at the time intensive treatment was initiated [15**]. Of the type 2 diabetes trials, UKPDS had the youngest patients with an average age of 53–54 at baseline, and treatment

started at the time of putative diagnosis of type 2 diabetes [12,13]. All the other trials had an older age and longer duration of disease prior to the initiation of treatment: ACCORD, average age 62 years, duration of disease 10 years [9**]; ADVANCE, 66 years and 8 years [10**]; and VADT, 60 years and 11.5 years [11**].

Degree of glycemic control

The ACCORD and VADT trials had the worst average glycemic control at the start of the trials with ACCORD having an average HbA1c of 8.3% [9**] and VADT 9.4% [11**]. Subjects in the other trials had much better glycemic control at the start – ADVANCE 7.5% [10**], UKPDS sulfonylurea 7.1%, UKPDS metformin 7.3% [12,13]. DCCT subjects, with type 1 diabetes, had an average HbA1c of 9.1% [15**].

Each study had different glycemic targets and achieved different results in different time frames. ACCORD and VADT had the greatest change in HbA1c for the intervention groups. The HbA1c in the intervention group in ACCORD started at 8.3% and reached 6.7% within 4 months and 6.4% within one year (compared to the conventional group which achieved HbA1c of 7.5% in 4 months and 1 year) [9**]. The HbA1c in VADT in the intervention group started at 9.4% and reached 6.9% within 6 months (compared to the conventional therapy group reaching 8.4%) [11**]. ADVANCE and UKPDS did not comment on how quickly the glycemic goals were reached, but the magnitude of change was less for both trials. The intervention and conventional groups in the UKPDS generally had higher levels of glycemia than the corresponding groups in the most recent trials, but still maintained HbA1c ≤ 8% in the conventional groups (see Table 1).

Hypoglycemia

Hypoglycemia was increased in all the intensive therapy groups. Considering only type 2 diabetes trials, rates of serious hypoglycemia were highest in the ACCORD and VADT trials. In ACCORD the rate of hypoglycemic events requiring medical assistance was 10.5% in the intensive treatment group compared to 3.5% in the conventional therapy group ($P < 0.001$) [9**]. In VADT, 24.5% of patients in the intensive treatment group had at least one serious adverse event related to hypoglycemia compared to 17.6% in the conventional therapy group ($P = 0.05$) [11**]. In ADVANCE 2.7% of the intensive group compared to 1.5% of the conventional therapy group had a severe hypoglycemic event ($P < 0.001$) [10**]. In UKPDS, the insulin treatment group had the most episodes of serious hypoglycemic events (mean proportion 2.3% per year over 10 years) followed by the sulfonylurea group (0.4–0.6% per year) [13].

Obesity and weight gain

The UKPDS metformin arm was specifically designed to include overweight patients, thus the mean baseline BMI for that study was 31.4 kg/m² [12], as opposed to the UKPDS sulfonylurea and insulin arms where the mean BMI was 27.5 [13]. The ACCORD and VADT trials also enrolled more overweight patients, with mean BMI in ACCORD at 32 kg/m² [9**] and VADT at 31 kg/m² [11**]. ADVANCE started with fewer overweight patients overall with an average BMI of 28 kg/m² [10**], and DCCT was 23 kg/m² [15**].

Subjects in the ACCORD and VADT trials had the greatest weight gain in the intervention groups. The ACCORD intensive group gained 3.5 kg, compared to 0.4 kg in the conventional group [9**]. The VADT intensive group gained 8.2 kg compared to 4.1 kg in the conventional group [11**]. The UKPDS trial also had significant weight gain in the insulin and sulfonylurea arms (insulin 4.0 kg, glibenclamide 1.7 kg, and chlorpropamide 2.6 kg) [13]. There was less difference in weight gain between groups in the ADVANCE and the UKPDS metformin study (ADVANCE −0.1 kg vs. −1 kg [10**]; UKPDS metformin: −1 kg/no change [12,16**]).

Other CV risk factors

Other CV risk factors tended to improve over the course of the studies and were better controlled at baseline in the more recent studies. Space constraints prevent detailed elaboration. In general, smoking decreased in all the studies over time. Lipid profiles and blood pressure improved over the course of all of the studies except for the DCCT without significant differences between intervention and conventional therapy groups.

Power and duration of follow-up

Because ACCORD was stopped early for safety issues, it had the shortest length of follow up with 3.5 years, though it was originally planned for 5.6 years [9**]. Stopping a trial early biases the results toward the stopping criteria because the full length of time for events to accrue is not maintained [20]. Also in ACCORD, the mortality in both the intervention and conventional therapy groups was lower than anticipated [9**]. Similarly, the annual rate of macrovascular events in ADVANCE was lower than expected (2.2% vs. the expected 3.0%), and the study protocol was altered after 3 years to increase its power by making the primary outcome a composite one and by extending the treatment and evaluation periods by 18 months [10**]. VADT, too, had fewer events in both the intervention and conventional therapy groups than predicted (predicted to have a 31.6% vs. 40% event rate; observed event rates were 33.5% and 29.5%) [11**]. UKPDS and DCCT were not powered to examine CV outcomes, but due to the long duration of follow-up in both cohorts, accrued sufficient events to yield informative data, with 21 years of follow-up of the UKPDS cohort [14**] and 17 years in the DCCT cohort [15**].

These lower than anticipated CV event rates reflect the success of more aggressive treatment of other CV risk factors. As a result, ACCORD, ADVANCE, and VADT were underpowered to detect differences in event rates in the time period of follow-up for each study. Given the results observed, it is not clear that longer follow-up would have reversed the trends seen, though such reversals of early trends have occurred [21]. In any case, the magnitude of potential benefit compared to harm did not appear to justify continuing the ACCORD trial or further altering the protocols of the other trials.

Summary: Implications for Practice

Given the differences among trials and the power caveats outlined above, taking the results of the trials at face value seems to show that older patients with a greater burden of preexisting CVD and longer duration of diabetes do not derive CV mortality benefit from TGC, and may experience harm, particularly if TGC is associated with weight gain and hypoglycemia. As the summary of the results of the trials demonstrates, ACCORD showed CV harm and the VADT trial showed no benefit with TGC. Compared to the other studies, these two trials had a higher proportion of patients with preexisting CVD, older patients, initiation of intensive treatment after a longer duration of diabetes, the highest starting HbA1c with reductions below currently recommended goals in the case of ACCORD, and the highest BMI with significantly more weight gain in the intensive groups of ACCORD and VADT. ADVANCE, which achieved a similar absolute level of glycemia as the ACCORD trial, showed no harm of TGC when achieved from a lower starting point and in the absence of hypoglycemia or significant weight gain.

By contrast, the results of the UKPDS and DCCT show that maintaining TGC soon after diabetes diagnosis appears to be beneficial. Notably, the level of glycemia achieved in the intervention group in both of these trials approached HbA1c of 7% rather than 6%. Subgroup analyses from the three negative RCTs, which should, of course, be interpreted with caution, seem to support this. In ACCORD there was some evidence that patients who did not have a

CV event prior to randomization or whose baseline HbA1c was $\leq 8.0\%$ may have had fewer fatal or nonfatal CV events than patients in the conventional group [9**]. A pos-hoc analysis of the VADT trial showed that TGC initiated later in the disease course (after 15 years) was not beneficial, but TGC initiated soon after diagnosis was beneficial [22**]. An ADA and ACC-AHA position statement found evidence to support aiming for HbA1c $< 7\%$ for prevention of microvascular disease and recommended that same goal to prevent macrovascular disease, particularly for newly diagnosed diabetics. They recommended less stringent HbA1c goals in patients who were at higher risk for hypoglycemia or have limited life expectancy, advanced complications, or extensive co-morbid conditions [23*].

While the studies summarized above have conflicting results, some themes emerge that are helpful in guiding therapy for patients. Overall, the rates of CV events in patients with diabetes are improving, likely due to aggressive control of other CV risk factors as has been shown to be effective in multiple clinical trials [24,25*]. Smoking cessation, and lipid, blood pressure and weight control should be emphasized in diabetes management. In terms of glycemic control, it is likely that TGC, aiming for HbA1c $\leq 7\%$, that is achieved without significant hypoglycemia or weight gain and is instituted early in the course of diabetes, will be beneficial. By contrast, the benefits of TGC may not extend to those with a long duration of diabetes or pre-existing CVD.

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References

1. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141:421–431. [PubMed: 15381515]
2. Moss SE, Klein R, Klein BE, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 1994;154:2473–2479. [PubMed: 7979844]
3. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991;81:1158–1162. [PubMed: 1951827]
4. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 2003;46:760–765. [PubMed: 12774166]
5. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. *Circulation* 2007;115:1544–1550. [PubMed: 17353438]
6. Dorman JS, Laporte RE, Kuller LH, et al. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study. Mortality results. *Diabetes* 1984;33:271–276. [PubMed: 6698317]
7. Libby P, Plutzky J. Diabetic macrovascular disease: the glucose paradox? *Circulation* 2002;106:2760–2763. [PubMed: 12450998]
8. Haffner SJ, Cassells H. Hyperglycemia as a cardiovascular risk factor. *Am J Med* 2003;115:6S–11S. [PubMed: 14678859]
9. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559. [PubMed: 18539917] (ACCORD) Study of intensive glucose control in subjects with established type 2 diabetes that showed increased cardiovascular mortality with HbA1c 6.4 compared to 7.5% at interim analysis, and was stopped before completion.
10. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572. [PubMed: 18539916] (ADVANCE). Study of intensive blood glucose control in established type 2 diabetes that showed benefit for microvascular (primarily reduction of macroalbuminuria), but not macrovascular events.
11. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139. [PubMed: 19092145] (VADT). Study of intensive glucose control in veterans with established type 2 diabetes and vascular disease that showed no benefit to intensive glucose control.

12. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865. [PubMed: 9742977]
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853. [PubMed: 9742976]
14. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589. [PubMed: 18784090] Ten-year follow up to the UKPDS study group, which showed benefit of intensive insulin therapy for macrovascular events, microvascular events, and all-cause mortality.
15. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653. [PubMed: 16371630] Long term follow up of the original DCCT study group, which showed benefit to intensive glycemic control for macrovascular events in patients with type 1 diabetes.
16. Kelly TN, Bazzano LA, Fonseca VA, et al. Glucose Control and Cardiovascular Disease in Type 2 Diabetes. *Ann Intern Med*. 2009 Meta-analysis of ACCORD, ADVANCE, VADT, and the original UKPDS metformin and sulfonylurea studies which showed a benefit of intensive glycemic control in non-fatal MI and cardiovascular events but not mortality.
17. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;373:1765–1772. [PubMed: 19465231] Meta-analysis of the original UKPDS trials, PROactive, ADVANCE, VADT, and ACCORD trials which showed a benefit of intensive glycemic control on coronary events but not mortality.
18. Abraira C, Duckworth W, McCarren M, et al. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. *J Diabetes Complications* 2003;17:314–322. [PubMed: 14583175]
19. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986. [PubMed: 8366922]
20. Tharmanathan P, Calvert M, Hampton J, Freemantle N. The use of interim data and Data Monitoring Committee recommendations in randomized controlled trial reports: frequency, implications and potential sources of bias. *BMC Med Res Methodol* 2008;8:12. [PubMed: 18366697]
21. DeMets DL, Pocock SJ, Julian DG. The agonising negative trend in monitoring of clinical trials. *Lancet* 1999;354:1983–1988. [PubMed: 10622312]
22. New Analyses Shed Further Light On VADT and ACCORD Trial Results. ADA 69th Scientific Sessions 2009 New Orleans ADA 16 Summary of symposium during the ADA 69th Scientific Sessions regarding VADT and ACCORD, where new analyses for VADT were presented that showed TGC instituted within 15 years of the diagnosis of diabetes reduced the risk of CVD and mortality, but TGC instituted 16–20 years after the diagnosis yielded no benefit, and TGC instituted >20 years of diagnosis increased risk of CV events. Also, new ACCORD analysis was presented that did not support the conclusion that low HbA1c levels were the cause of the increased mortality during the trial.
23. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009;119:351–357. [PubMed: 19095622] Summary of the recommendations from the ADA, ACC, and AHA which include continued HbA1c targets of <7.0% for most patients unless higher risk for hypoglycemia, have limited life expectancy, advanced complications or extensive co-morbid conditions.
24. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016. [PubMed: 12814710]
25. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–591. [PubMed: 18256393] (Steno-2). Multi-faceted intervention targeting hyperglycemia, hypertension, hyperlipidemia and

microalbumuria, also including secondary prevention of CVD with aspirin that demonstrated a decrease in mortality, cardiovascular, and microvascular events.

Table 1

Trial and patient characteristics

Trial	DM Type	Duration of follow up, years	N in the intervention group / N in the conventional group	Age, years	Duration of DM prior to trial enrollment, years	Percent of subjects with CVD at start of trial	Mean starting HbA1c (%) intervention / conventional	Ending HbA1c (%) intervention / conventional	Weight gain intervention / conventional
ACCORD, 2008 [9]	2	3.5 *	5128 / 5123	62.2	10	35	8.3 / 8.3	6.4 / 7.5 **	+3.5 kg / +0.4 kg
ADVANCE, 2008 [10]	2	5 **	5571 / 5569	66	8	12 MI 32 MI, stroke, other	7.5 / 7.5	6.5 / 7.3 *	-0.1 kg / -1 kg
VADT, 2009 [11]	2	5.6 **	892 / 899	60.4	11.5	40	9.4 / 9.4	6.9 / 8.4 **	+8.2 kg / +4.1 kg
UKPDS sulfonylurea, 2008 [13,14]	2	Original trial: 11.1 ** Total follow up: 21 **	Original trial: 2729 / 1138 Observational follow up: 2118 / 880	54 **	0 (newly diagnosed)	Excluded MI in last year, current angina/HF, ≥1 vascular events	7.1 / 7.1	Original trial: 7.0 / 7.9 ** Observational follow up: 7.9 / 8.5 **	+2.7 kg / +0.9 kg
UKPDS metformin, 2008 [12,14]	2	Original trial: 10.7 ** Total follow up: 21 **	Original trial: 342 / 411 Observational follow up: 279 / 309	53	0 (newly diagnosed)	Excluded MI in last year, current angina/HF, ≥1 vascular events	7.3 / 7.1	Original trial: 7.4 / 8.0 ** Observational follow up: 8.4 / 8.9 **	-1 kg / 0 kg
DCCT, 2005 [15]	1	Original trial: 6.5 * Total follow up: 17 *	Original trial: 711 / 730 Observational follow up: 593 / 589	27	5.5	Excluded	9.1 / 9.1	7.9 / 7.8 *	+5.1 / +4.2 ***

DM=Diabetes mellitus. MI = myocardial infarction CVD=Cardiovascular disease. HF=Heart failure. HbA1c=Hemoglobin A1c.

* Mean

** Median

*** Change in BMI, kg/m²

Table 2

Trial outcomes

	Primary outcome	Death from CVD intensive / conventional	Nonfatal MI interventional / conventional	Nonfatal stroke interventional / conventional	Death from any cause
ACCORD, 2008 [9]	First occurrence of nonfatal MI or nonfatal stroke or death from CVD (MI, CHF, arrhythmia, invasive CV interventions, CV causes after non-CV surgery, stroke, unexpected death presumed to be from ischemic CVD occurring with 24 hours after onset of symptoms, death from other vascular disease)	2.6% / 1.8% P=0.02	3.6% / 4.6% P=0.004	1.3% / 1.2% P=0.74	5.0% / 4.0% P=0.04
ADVANCE, 2008 [10]	Composite of macrovascular and microvascular events: Macrovascular – death from CV causes, nonfatal MI, nonfatal stroke Microvascular – new / worsening nephropathy, retinopathy	4.5% / 5.2%	2.7% / 2.8%	3.8 / 3.8%	8.9% / 9.6% P=0.28
VADT, 2009 [11]	Time to first occurrence of any one of a composite of CVD (MI, stroke, death from CVD, new or worsening CHF, surgical intervention for cardiac, cerebrovascular or PVD, inoperable CAD, amputation for ischemic gangrene)	4.5% / 3.7%	0.91 / 0.90 P =0.24 *	0.96 / 0.95 P=0.32 *	11.4% / 10.6% P=0.62
UKPDS sulfonylurea, 2008 [14]	7 outcomes: 1 Any diabetes related end-point 2 Diabetes-related death 3 Death from any cause 4 MI (fatal and non-fatal) 5 Stroke (fatal and non-fatal) PVD 6 PVD 7 Microvascular disease		24.8% / 28% P=0.01	9.5% / 10.2% ***	42.6% / 47.2% P=0.007
UKPDS metformin, 2008 [14]	7 outcomes, as above.		38.8% / 48% P=0.005	9.9% / 10.2% ***	44.4% / 52.8% P=0.002
DCCT, 2005 [15]	Time to first CVD event: nonfatal MI or stroke, death from CVD, subclinical MI, angina, confirmed ischemic changes on exercise tolerance testing or by clinically significant obstruction on coronary angiography or need for revascularization	1 vs. 3 events	7 vs. 16 events	1 vs. 5 events	57% risk reduction of first non-fatal MI, stroke or death P=0.02

If no p-values are listed, none were available

* 6-year event rate
** Includes fatal MI
*** Includes fatal stroke