The effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials

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Abstract

Background: Intensive glucose control is understood to prevent complications in adults with type 2 diabetes. The aim of this study was to more precisely estimate the effects of more, compared with less, intensive glucose control on the risk of microvascular events.

Methods: Meta-analyses of individual participant data from large-scale randomised controlled trials of glucose lowering using pre-specified and standardised kidney (a composite of end-stage kidney disease, renal death, development of an eGFR < 30ml/min/1.73m^2 or development of overt diabetic nephropathy), eye (a composite of requirement for retinal photocoagulation therapy or vitrectomy, development of proliferative retinopathy or progression of diabetic retinopathy) and nerve (a composite of new loss of vibratory sensation, ankle reflexes or light touch) outcome definitions. Overall estimates of effect were calculated with a random-effects model.

Findings: A total of 27,049 participants from 4 trials contributed 1,626 kidney events, 795 eye events and 7,598 nerve events over a median of 5.0 (inter-quartile interval: 4.5, 5.0) years follow up. Assignment to more, compared with less, intensive glucose control resulted in a 0.90% (95%CI 0.58, 1.22) absolute difference in mean HbA_{1c}, with significant relative risk reductions of kidney and eye events by 20% (HR 0.80; 0.72, 0.88; p<0.001) and 13% (HR 0.87; 0.76, 1.00; p=0.042) respectively, but not nerve events (HR 0.98; 0.87, 1.09; p=0.679).

Interpretation: More, compared with less, intensive glucose control over 5 years reduced both kidney and eye events. Glucose lowering remains important for the prevention of long-term microvascular complications in adults with type 2 diabetes.

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Research in context

Question: Does more, compared with less, intensive glucose control reduce the risk of serious kidney, eye and nerve events in adults with type 2 diabetes?

Findings: In this first meta-analysis of individual participant data from large-scale randomised controlled trials of glucose lowering, more compared with less intensive glucose control reduced kidney and eye events but not nerve events.

Meaning: Glucose lowering remains important for the prevention of the long-term kidney and eye complications of type 2 diabetes.

Introduction

Diabetes mellitus is one of the most common non-communicable diseases.[1] The evidence for the devastating long-term effects of diabetes is overwhelming and includes deterioration in kidney function retinal damage and cataracts, and nerve damage. These in turn contribute to development of severe clinical complications including end stage kidney disease, blindness and ulceration and amputation.[1,2] Along with blood pressure and lipid management, improved glucose control has been a treatment mainstay in the management of diabetes, and the past decade has seen exponential growth in the number of pharmacological and non-pharmacological strategies to control glucose levels. Despite the growth in therapeutic options, uncertainty surrounds the clinical benefits (and risks) of varying intensities of glucose-control for patients with type 2 diabetes.[3-7] Evidence from large clinical trials[8-11], taken individually, has been insufficient to reliably inform clinical practice and treatment guidelines. In addition, previous systematic reviews and meta-analyses have been limited to pooling of published data without use of consistent and standardised definitions of exposures and outcomes.[4-7] In response, diabetes and glucose outcomes trialists formed CONTROL (Collaborators on Trials of Glucose Lowering), an international collaboration. Established in 2008, CONTROL seeks to provide reliable evidence for clinicians and patients about the effects of more, compared with less, intensive glucose control through informed, pre-specified collaborative meta-analyses of individual participant data from all eligible, large-scale randomised trials. The first set of analyses, based on tabular data from more than 27,000 patients with type 2 diabetes from North America, UK, Europe and Asia Pacific, reported that more intensive glucose control produced a modest but significant reduction in major cardiovascular events (HR 0.91 95%CI 0.84-0.99), no

reduction in all-cause mortality and an increase in severe hypoglycaemia (HR 2.48 95%CI 1.91-3.21).[12] In this second set of analyses, based on individual participant data from four large trials [8-11], we examine the effects of more compared with less intensive glucose control on the risk of those long-term consequences that are typically described as "microvascular events" – *i.e*. involving the kidneys, eyes and nerves.

Methods

Trial inclusion and exclusion criteria

The detailed search strategy, methods, key characteristics and risk of bias of the included trials have been published previously.[12] An updated search was performed for the period from February 2009 to January 2017 to determine if any additional trials met the inclusion and exclusion criteria (Supplementary Appendix 1).

In brief, trials were included if they satisfied the following criteria: were randomised and controlled and designed to separately assess the effects of assigning adult patients with type 2 diabetes to lower versus higher HbA_{1c}, fasting and/or post-load glucose targets; large size, defined as at least 1000-patient-years of follow-up in each treatment arm and a minimum of 2 years average follow-up on randomised treatment; double blind or open label and used prospectively defined, *i.e.* pre-specified, outcomes; conducted using an intention-to treat approach and achieved ≥90% follow up of randomised patients for vital status. Trials were excluded if they randomised patients to multi-factorial interventions (except where factorial randomisation allowed the separate assessment of the effects of glycaemic control); studied patients in high-dependency or critical care settings; or studied patients with acute myocardial

infarction or with acute coronary syndromes receiving invasive management strategies such as coronary revascularisation.

Study Outcomes

All outcomes were pre-specified in the study protocol for this meta-analysis (Supplementary Appendix). The primary outcomes were 1) kidney events, defined as a composite of end-stage kidney disease (dialysis or renal transplantation), renal death, development of an eGFR < 30ml/min/1.73m^2 (calculated on at least 2 consecutive visits post-randomisation using the MDRD formula) or development of overt diabetic nephropathy (normo- or micro- to sustained macroalbuminuria i.e. an albumin:creatinine ratio > 300 mg albumin per gram creatinine recorded on at least 2 consecutive visits post-randomisation); 2) eye events defined as a composite of requirement for retinal photocoagulation therapy or vitrectomy, development of proliferative retinopathy (new blood vessels on the disc or elsewhere, vitreous haemorrhage, pre-retinal haemorrhage, or fibrous proliferations on the disc or elsewhere) or progression of diabetic retinopathy by at least 3 steps on the ETDRS severity scale; and 3) nerve events defined as a composite of new loss of vibratory sensation (both feet), new loss of ankle reflexes (both legs) or new loss of light touch (loss of pressure sensation with 10gm force monofilament).

The secondary outcomes were the individual components of each of the 3 primary outcomes as well as development or progression of albuminuria (microalbuminuria or macroalbuminuria), maintenance or regression to normoalbuminuria, development of macular oedema, development of diabetes-related blindness, vision deterioration and cataract extraction.

Data collection

A dataset of de-identified individual participant data, as per the pre-specified variable definitions, was provided by each trial. These were collated and summary statistics and hazard ratios for endpoints calculated and shared with each trial to allow collaborators to cross-check the data and analyses. The data collected comprised key baseline characteristics, selected characteristics during follow-up and outcome events by randomised group. No important issues with the data integrity were identified.

Statistical analysis

Baseline characteristics were analysed by treatment group with discrete variables summarised by frequencies and percentages and continuous variables as either mean and SD or median and interquartile interval Q1, Q3). Chronic kidney stage was classified using the Kidney Disease Outcomes Quality Initiative (K/DOQI) definition based on eGFR level.[13] Differences in achieved $HbA_{1c,}$ fasting plasma glucose and other cardiovascular risk factors were investigated using linear mixed models for each trial, accounting for repeat measurements over time, and pooled using a random-effects model.

Analyses for each clinical outcome were based on the time to the first relevant event experienced by the participant. Approximately 5 years of follow-up (the UKPDS trial follow up was truncated at 5 years) was analysed to provide a similar observation period across all trials.

Effects of randomised treatment on primary outcomes were assessed using Cox proportional hazards models, with hazard ratios and 95% CIs calculated separately for each trial, using an intention-to-treat approach. Overall estimates of effect were calculated with a random-effects model, in which the log relative risk for every trial was weighted by the reciprocal of the variance of the log relative risk. The

homogeneity of treatment effects across trials was estimated for the major outcomes using the I^2 statistic and Cochran's Q test.

Pre-defined subgroup analyses were performed by sex, age (divided at both the mean and median), baseline HbA_{1c} (<7.5%, 7.5-8.5%, >8.5%), race (Caucasian, Asian, Hispanic, Black), duration of diabetes (<5 years, ≥5 years), pre-existing cardiovascular disease and thirds of estimated glomerular filtration rate (eGFR). Consistency in treatment effects across the subgroups was tested using χ^2 tests of homogeneity.

Analyses for secondary outcomes and for subgroups should be regarded as exploratory because no adjustments for multiple comparisons were made. Analyses were carried out using STATA (Release 9.2; Stata Corporation, College Station, TX, USA).

Sensitivity analyses examined 1) using the CKD-Epi formula rather than MDRD formula to calculate eGFR in the outcomes, 2) substituting development of doubling of serum creatinine for development of an eGFR<30 ml/min/m^2 and 3) substituting development of an eGFR reduction of 40% for development of an eGFR<30 ml/min/m^2.

Results

Only four trials satisfied the study inclusion criteria: Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, United Kingdom Prospective Diabetes Study (UKPDS) and the Veterans Administration Diabetes Trial (VADT) (Supplementary Appendix 2). As previously reported, in the

ACCORD study the intensive glucose lowering intervention was stopped after a mean of 3.7 years due to a mortality signal.[9] For the next 1.2 years, all ACCORD participants received the standard (non-intensive) glucose lowering intervention and contributed microvascular and other outcomes to the database.

Altogether, these 4 trials randomized 27,049 adults with type 2 diabetes to either more or less intensive glucose control and followed them for a median (IQR) of 5.0 (4.5-5.0) years (Table 1). The mean age of participants ranged from 53.3 years (UKPDS) to 65.8 years (ADVANCE) and the median duration of diabetes ranged from 0 years (UKPDS) to 10 years (ACCORD and VADT) (Table 1). The baseline mean HbA_{1c} level of participants ranged from 7.0% (UKPDS) to 9.4% (VADT). At the completion of follow up the ADVANCE, VADT and UKPDS participants who were allocated to more intensive control were taking more glucose lowering therapies than were those allocated to less intensive control (Supplementary Table 1). Glucose lowering therapies did not differ within the ACCORD trial groups at 5 years because of relaxation of the intensity of glucose control after a mean of 3.7 years (Supplementary Table 1).

Effects on glucose control and other clinical parameters

Allocation to more compared with less intensive glucose control resulted in a pooled absolute difference in mean HbA_{1c} (%) of 0.90% (95% CI 0.58, 1.22) and a pooled absolute difference in fasting plasma glucose (mmol/l) of 1.69 mmol/l (95% CI 1.26, 2.12) (Table 2). The achieved mean HbA_{1c} levels were 6.80% (95% CI 6.65, 6.95) and 7.74% (95% CI 7.34, 8.14) for more versus less intensive glucose control groups, respectively. Small between-group differences in BMI and waist circumference were also evident.

Effects on major kidney, eye and nerve outcomes

During the follow up period, 1,626 primary kidney events 795 primary eye events and 7598 primary nerve events were recorded.

More intensive glucose control was associated with a relative risk reduction of the composite primary kidney outcome of 20% (HR 0.80, 95% CI 0.72, 0.88, p<0.001) (Figure 1). This effect was primarily driven by reduced risks of development of overt nephropathy (macroalbuminuria) but also non-significant reduction in risks of ESKD and renal death (Figure 2). Intensive glucose control also reduced the risk of development of microalbuminuria and increased the odds of regression of albuminuria (from both micro- to normoalbuminuria and macro- to micro- or normoalbuminuria), and of maintaining normoalbuminuria. There was no evidence of heterogeneity in the effects between trials (I^2=0.0%).

When the CKD-Epi rather than the MDRD formula was used to calculate eGFR the results were unchanged for the primary kidney outcome (Supplementary Table 2). Additionally, when eGFR<30 ml/min/m^2 was replaced by doubling of serum creatinine or eGFR reduction of 40% in the composite primary kidney outcome, the results were unchanged (Supplementary Table 2). Intensive glucose control did not significantly reduce the risk of development of an eGFR<30 ml/min/m^2 (Figure 2) or development of doubling of serum creatinine or an eGFR reduction of 40% (Supplementary Table 2).

More intensive glucose control was associated with a relative risk reduction of the composite primary eye outcome of 13% (HR 0.87, 95% CI 0.76, 1.00, p=0.042) (Figure 1). This effect was primarily driven by reduced risk of progression of retinopathy (ETDRS). Intensive glucose control also reduced risks of the other

secondary eye endpoints of macular oedema and need for cataract extraction (Figure 3). There was no evidence of heterogeneity in the effects between trials (I^2=0.0%). With the accumulation of sufficient events over time, the effects on the composite primary kidney and eye outcomes emerge in the third and fifth years of follow up respectively (Supplementary Table 3).

More intensive glucose control did not reduce the risk of the composite primary nerve endpoint (HR 0.98 95% CI 0.87, 1.09, p=0.679) (Figure 1, Supplementary Table 3). There was significant heterogeneity in the effects among trials (I^2=78.1%) with the risk reduced by 8% in ACCORD (HR 0.92, 95%CI 0.87, 0.98) but not in the other trials. When each nerve event was considered separately, no reduced risks of loss of vibratory sensation, loss of ankle reflexes or loss of light touch were evident (Supplementary Figure 1).

Sub-group analyses

The effect of more intensive glucose control on the composite primary kidney, eye and nerve endpoints was consistent across pre-specified participant subgroups (Supplementary Fig. 2A-C) with one exception: for the eye endpoint, male participants appeared to benefit from more intensive glucose control whereas female participants did not (p for homogeneity = 0.04).

Absolute treatment effects

The absolute event rates are shown in Figure 1. Across the overall trial population, 73 (95%CI 52-122) and 63 (95%CI 34-1617) individuals would need to be treated (NNT) for approximately 5 years with intensive glucose control to prevent one primary kidney or one primary eye event, respectively.

Discussion

In this individual participant data meta-analysis of large-scale randomised glucose trials comparing more with less intensive glucose control in patients with type 2 diabetes, a modest achieved HbA_{1c} absolute difference of 0.9% substantially reduced the risk of kidney and eye events but not nerve events over a median of 5 years. The composite primary kidney outcome, including development of overt nephropathy (macroalbuminuria), ESKD and renal death, was reduced by 20% and the composite primary eye outcome, including development and progression of retinopathy, was reduced by 13%. These effects translate into a need to treat between 63 to 73 patients with type 2 diabetes in order to prevent one kidney or eye event.

As noted above, these findings are based on 5 years of follow-up in all 4 trials. In 3 of these trials, participants were allocated to more versus less intensive glucose lowering for approximately 5 years, whereas in the ACCORD trial the active intervention period lasted for a mean of 3.7 years. As such, the ACCORD results and the analyses as a whole may modestly underestimate the effect of a full 5 years of more versus less intense glucose control on microvascular outcomes.

Improvements in the management of cardiovascular disease over the last 2 decades have resulted in major reductions in the rates of acute myocardial infarction and stroke among populations with diabetes.[2] However, the same magnitude of reduction in the rate of ESKD has not been observed among populations with diabetes and the increasing prevalence of diabetes will probably see the absolute number of events increase.[2,14] Given this rising burden of disease, a refocus on glycaemic control may be warranted. Indeed, our findings support the need for more intensive glycaemic

targets if future rates of kidney and eye complications in type 2 diabetes are to be minimized.

The beneficial effects of intensive glucose control on kidney and eye outcomes were more modest than those reported by epidemiological studies.[15-16] This discordance has previously been reported for macrovascular outcomes.[12,16] Individual participant data from meta-analyses of well-designed robust clinical trials such as this provide the most precise estimates of treatment effect because they are based on larger event numbers. No heterogeneity in the effects across trials was evident for these outcomes. Given the detection of even modest treatment effects may translate into prevention of many serious complications globally, these findings have major implications for treatment recommendations. However, the potential benefits of intensive glucose control must be balanced against the increased risk of severe hypoglycaemia, [4-11] particularly in those patients at greater risk, such as those with advanced age and comorbidities.[18]

In contrast, intensive glucose control did not reduce the primary nerve outcome. Substantial heterogeneity in the effects among trials was evident, suggesting that the magnitude of the effects may differ depending on the components and measurement of this outcome. For example, the effects on loss of vibratory sensation and light touch appeared greater than the effect on loss of ankle jerks. The absence of a benefit to nerve related outcomes may be due to the fact that nerve events were assessed using subjective and variable methods. The findings may have differed had standardized nerve conduction testing been applied in all 4 trials.

Pre-specified subgroup analyses of the effects of more intensive glucose control on the composite primary kidney, eye and nerve outcomes showed no significant

differences with respect to age, baseline HbA1c, ethnicity, duration of diabetes, pre-existing cardiovascular disease and level of eGFR. Although of borderline significance, there was a suggestion that male participants achieved benefit for eye outcomes whereas female participants did not. This finding needs to be considered with caution in light of its exploratory nature and the large number of tests performed.

The strengths of this meta-analysis include collaboration of the original trial groups to produce individual participant data of the highest quality, the large size of the trials, the focus on directly comparable pre-specified risk exposures and key major outcomes (using the same definitions), and the opportunity for the original trial groups to independently verify the pooled results. The limitations include the small number of trials and limited ability to perform subgroup analyses and meta-regression in order to understand the effects in particular patient groups as well as explore heterogeneity among trials for some outcomes. Additionally, the low event rates for the more serious clinical components, such as ESKD and renal death (fewer than 250 ESKD events and 40 renal death events), reduced the power for separately significant effects to be observed for these outcomes and meant the primary kidney outcome was primarily driven by the more common event of development of macroalbuminuria. Finally, the absolute treatment effects and NNTs need to interpreted with caution given they are unlikely to be generalisable to other, unselected populations with type 2 diabetes.

Conclusions

Intensification of glucose control for a median of 5 years reduced both kidney and eye events but not nerve events among adults with type 2 diabetes. Glucose management

remains an important treatment for the prevention of the long-term complications of diabetes.

Contributors

SZ, HA, TC, RC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SZ coordinated the study. SZ, HA, HG, RH, MW, PR, RH and JC co-designed the study. All contributed to the interpretation of the findings. All authors critically reviewed the report. No writing assistance was provided.

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Disclosures

SZ reports past participation in advisory boards and/or receiving honoraria from Amgen Australia, AstraZeneca /Bristol-Myers Squibb Australia, Janssen-Cilag, Merck Sharp & Dohme (Australia), Novartis Australia, Sanofi, Servier Laboratories and Takeda Australia as well as Monash University undertaking contract work for AstraZeneca Pty Ltd/Bristol-Myers Squibb Australia Pty Ltd; HCG has received grant support from Sanofi, Lilly, AstraZeneca and Merck, honoraria for speaking from Sanofi, Novo Nordisk, AstraZeneca and Berlin Chemie, and consulting fees from Sanofi, Lilly, AstraZeneca, Merck, Novo Nordisk, Abbot, Amgen, Boehringer Ingelheim, and Kaneq Bioscience; RRH has received grants and personal fees from Merck and Co., Inc.; grants for investigator-led studies from Bayer and AstraZeneca; and personal fees from Bayer, Intarcia, Novartis, Novo Nordisk, Servier and other support from GlaxoSmithKline, Janssen, and Takeda; MW is a consultant to Amgen; JC has received research grants from the NHMRC and from Servier, administered through the University of Sydney, as Principal Investigator for the ADVANCE trial and the ADVANCE-ON post-trial follow-up study, as well honoraria from Servier for speaking about these studies at scientific meetings.

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Tables

Table 1. Baseline participant characteristics and study follow-up

	ACCORD (n=10251)	ADVANCE (n=11140)	UKPDS (n=3867)	VADT (n=1791)
Demographics				
Age (years)	62.2 (6.8)	65.8 (6.4)	53.3 (8.6)	60.4 (8.7)
Female	3952 (39%)	4733 (42%)	1502 (39%)	52 (3%)
Age when diabetes first diagnosed (years)	51.4 (9.3)	57.8 (8.7)	52.6 (8.6)	48.9 (10)
Duration of known diabetes (years)	10 (5 to 15)	7 (3 to 11)	0 (0 to 0)	10 (6 to 16)
Prior vascular disease				
History of macrovascular disease	3609 (35%)	3590 (32%)	66 (2%)	723 (40%)
History of microvascular disease	3953 (39%)	1155 (10%)	42 (1%)	152 (8%)
Glycaemic control				
HbA1c (%)	8.3 (1.1)	7.5 (1.6)	7 (1.5)	9.4 (1.5)
HbA1c (%)	8.1 (7.6 to 8.9)	7.2 (6.5 to 8.2)	6.8 (5.9 to 7.9)	9.1 (8.3 to 10.2)
Fasting plasma glucose (mmol/l)	9.7 (3.1)	8.5 (2.8)	8.4 (2.3)	11.4 (3.8)
Fasting plasma glucose (mmol/l)	9.3 (7.7 to 11.3)	7.9 (6.6 to 9.7)	7.9 (6.7 to 9.7)	10.8 (8.6 to 13.7)
Other major risk factors				
Systolic BP (mmHg)	136.4 (17.1)	145 (21.5)	134.9 (19.3)	131.6 (16.7)
Diastolic BP (mmHg)	74.9 (10.7)	80.6 (10.9)	82.3 (10.1)	76.1 (10.3)
Total cholesterol (mmol/l)	4.7 (1.1)	5.2 (1.2)	5.4 (1.1)	4.7 (1.2)
LDL-cholesterol (mmol/l)	2.7 (0.9)	3.1 (1.0)	3.5 (1.0)	2.8 (0.8)
HDL-cholesterol (mmol/l)	1.1 (0.3)	1.3 (0.4)	1.1 (0.2)	0.9 (0.3)
Triglycerides (mmol/l)	1.8 (1.2 to 2.6)	1.6 (1.2 to 2.3)	1.5 (1.1 to 2.1)	1.8 (1.3 to 2.7)
BMI (kg/m^2)	32.2 (5.5)	28.3 (5.2)	27.5 (5.1)	31.2 (4.4)
Current smoking	1429 (14%)	1550 (14%)	1190 (31%)	299 (17%)
Microalbuminuria	2504 (25%)	2857 (27%)	368 (10%)	569 (33%)

eGFR (ml/min/m^2)	83.6 (23.1)	73.6 (23.3)	79.6 (17.0)	82.2 (22.0)
K/DOQI CKD stage				
Stage G1	3244 (32%)	1888 (17%)	941 (25%)	509 (28%)
Stage G2	5717 (56%)	6379 (57%)	2501 (65%)	1037 (58%)
Stage G3a	1005 (10%)	2251 (20%)	341 (9%)	229 (13%)
Stage G3b	219 (2%)	504 (5%)	53 (1%)	15 (1%)
Stage G4	5 (0%)	69 (1%)	5 (0%)	0 (0%)
Stage G5	1 (0%)	5 (0%)	0 (0%)	0 (0%)
Study follow-up				
Median (IQR) (years)	5.0 (4.1 to 5.0)	5.0 (4.7 to 5.0)	5.0 (5.0 to 5.0)	4.9 (4.9 to 5.0)

Data are n (%), mean (SD), or median (IQR). K/DOQI, Kidney Disease Quality Outcome Initiative.[10]

Table 2. Mean differences in cardiovascular risk factors between randomized groups (more versus less intensive glucose control) during follow-up

	ACCORD		ADVANCE		UKPDS		VADT		Overall	
	mean	**SE**	**mean**	**SE**	**mean**	**SE**	**mean**	**SE**	**mean (95%CI)***	**I^2**
Glycaemic control										
HbA1c (%)	-1.01	0.02	-0.52	0.03	-0.73	0.06	-1.34	0.07	-0.90 (-1.22 to -0.58)	98.8%
Fasting plasma glucose (mmol/l)	-1.89	0.06	-1.16	0.05	-1.62	0.09	-2.16	0.19	-1.69 (-2.12 to -1.26)	96.6%
Other major risk factors										
Systolic BP (mmHg)	-0.48	0.34	-1.59	0.35	0.72	0.50	-0.27	0.74	-0.46 (-1.44 to 0.53)	80.0%
Diastolic BP (mmHg)	-0.49	0.19	-1.10	0.18	0.42	0.30	-0.49	0.44	-0.44 (-1.07 to 0.19)	84.6%
Total cholesterol (mmol/l)	-0.03	0.02	-0.11	0.02	-0.11	0.03	-0.02	0.05	-0.08 (-0.12 to -0.03)	68.5%
LDL-cholesterol (mmol/l)	0.02	0.02	-0.05	0.02	-0.04	0.03	0.06	0.04	-0.01 (-0.05 to 0.04)	74.2%
HDL-cholesterol (mmol/l)	0.02	0.00	-0.01	0.01	-0.02	0.01	0.00	0.01	0.00 (-0.02 to 0.02)	92.7%
Triglycerides (log-transformed, mmol/l)	-0.09	0.01	-0.08	0.01	-0.05	0.01	-0.09	0.02	-0.08 (-0.10 to -0.06)	66.6%
BMI (kg/m2)	0.85	0.08	0.19	0.04	0.65	0.06	0.85	0.10	0.63 (0.27 to 0.99)	97.3%
Waist (cm)	1.35	0.13	0.30	0.12	1.36	0.50	2.09	0.33	1.24 (0.44 to 2.03)	94.1%

* Differences were investigated using linear mixed models for each trial, accounting for repeat measurements over time, and pooled using a random-effects model.

Supplementary Table 1. Drug treatments at baseline and follow-up

	ACCORD (n=10251)		ADVANCE (n=11140)		UKPDS (n=3867)		VADT (n=1791)	
	Less intensive	**More intensive**	**Less intensive**	**More intensive**	**Less intensive**	**More intensive**	**Less intensive**	**More intensive**
Baseline								
Sulfonylurea	2529 (50%)	2607 (51%)	3927 (71%)	3972 (71%)	0 (0%)	0 (0%)	561 (62%)	529 (59%)
Metformin	3076 (60%)	3059 (60%)	3355 (60%)	3397 (61%)	0 (0%)	0 (0%)	632 (70%)	605 (68%)
Thiazolidinedione	983 (19%)	999 (19%)	206 (4%)	201 (4%)	0 (0%)	0 (0%)	171 (19%)	166 (19%)
Acarbose	35 (1%)	34 (1%)	448 (8%)	512 (9%)	0 (0%)	0 (0%)	16 (2%)	20 (2%)
Glinide	90 (2%)	96 (2%)	84 (2%)	103 (2%)	0 (0%)	0 (0%)	4 (0%)	5 (1%)
Insulin	1832 (36%)	1750 (34%)	77 (1%)	82 (1%)	0 (0%)	0 (0%)	472 (53%)	466 (52%)
Blood pressure lowering agent	4252 (83%)	4225 (82%)	4182 (75%)	4183 (75%)	216 (19%)	536 (20%)	755 (84%)	748 (84%)
Lipid lowering agent	3440 (67%)	3433 (67%)	1953 (35%)	1981 (36%)	N/A	N/A	591 (66%)	595 (67%)
Antiplatelet agent	2874 (56%)	2911 (57%)	2582 (46%)	2617 (47%)	160 (15%)	449 (17%)	685 (76%)	681 (76%)
Anticoagulant agent	165 (3%)	156 (3%)	192 (3%)	216 (4%)	N/A	N/A	N/A	N/A
End of follow-up								
Sulfonylurea	2407 (48%)	1778 (36%)	3245 (59%)	4939 (90%)	197 (27%)	885 (54%)	398 (44%)	472 (53%)
Metformin	3375 (68%)	3473 (70%)	3599 (66%)	3951 (72%)	68 (9%)	159 (10%)	486 (54%)	534 (60%)
Thiazolidinedione	1245 (25%)	1397 (28%)	578 (11%)	895 (16%)	N/A	N/A	265 (29%)	337 (38%)
Acarbose*	151 (3%)	287 (6%)	640 (12%)	972 (18%)	N/A	N/A	20 (2%)	93 (10%)
Glinide	429 (9%)	745 (15%)	145 (3%)	70 (1%)	N/A	N/A	2 (0%)	10 (1%)
Insulin	2731 (55%)	3270 (66%)	1326 (24%)	2205 (40%)	104 (9%)	544 (20%)	689 (77%)	770 (86%)
Blood pressure lowering agent	4395 (88%)	4277 (86%)	4412 (80%)	4374 (80%)	637 (56%)	1594 (58%)	665 (74%)	659 (74%)
Lipid lowering agent	3909 (79%)	3873 (78%)	2801 (51%)	2739 (50%)	N/A	N/A	579 (64%)	582 (65%)
Antiplatelet agent	3135 (63%)	3077 (62%)	3216 (59%)	3302 (60%)	66 (9%)	119 (7%)	818 (91%)	813 (91%)

Anticoagulant agent	301 (6%)	253 (5%)	3216 (59%)	3302 (60%)	N/A	N/A	N/A	N/A

Data are n (%), mean (SD), or median (IQR). *Defined in ACCORD at baseline as any alpha glucosidase inhibitor use. N/A indicates not available.

Supplementary Table 2. Effects of more versus less intensive glucose control on additional kidney events

	ACCORD HR (95%CI)	**ADVANCE** HR (95%CI)	**UKPDS** HR (95%CI)	**VADT** HR (95%CI)	**Overall**
Primary kidney outcome					
eGFR <30 (MDRD)	0.79 (0.69, 0.90)	0.77 (0.65, 0.91)	0.98 (0.71, 1.35)	0.70 (0.39, 1.28)	0.80 (0.72, 0.88)
eGFR <30 (CKD-Epi)	0.79 (0.69, 0.90)	0.77 (0.65, 0.91)	1.03 (0.75, 1.40)	0.73 (0.40, 1.34)	0.80 (0.73, 0.88)
eGFR <30 replaced with doubling of serum creatinine	0.79 (0.69, 0.89)	0.80 (0.68, 0.93)	0.97 (0.73, 1.30)	0.75 (0.43, 1.29)	0.81 (0.73, 0.88)
eGFR <30 replaced with reduction of eGFR of 40%	0.86 (0.77, 0.96)	0.85 (0.75, 0.97)	0.89 (0.67, 1.18)	0.86 (0.60, 1.24)	0.86 (0.80, 0.93)
Secondary kidney outcomes					
eGFR <30 (MDRD)	1.34 (0.94, 1.91)	1.09 (0.81, 1.48)	0.55 (0.12, 2.46)	1.02 (0.47, 2.21)	1.16 (0.93, 1.44)
eGFR <30 (CKD-Epi)	1.41 (0.98, 2.02)	1.08 (0.80, 1.47)	0.83 (0.15, 4.52)	1.11 (0.51, 2.43)	1.19 (0.96, 1.49)
Doubling of serum creatinine	1.04 (0.80, 1.35)	0.91 (0.71, 1.17)	0.80 (0.41, 1.56)	1.02 (0.51, 2.04)	0.96 (0.81, 1.14)
Reduction of eGFR of 40%	1.04 (0.89, 1.21)	0.99 (0.84, 1.17)	0.54 (0.30, 0.99)	0.95 (0.65, 1.38)	0.97 (0.84, 1.12)

Supplementary Table 3. Effects of more versus less intensive glucose control on the primary outcomes by years of follow up

	Event number		Pooled HR (95%CI)	p value
	More intensive	Less intensive		
Primary kidney outcome				
0-1 years	120	112	1.04 (0.60 to 1.79)	0.896
0-2 years	264	279	0.84 (0.68 to 1.04)	0.102
0-3 years	408	456	0.79 (0.69 to 0.91)	0.001
0-4 years	584	655	0.80 (0.72 to 0.90)	<0.001
0-5 years	761	865	0.80 (0.72 to 0.88)	<0.001
Primary eye outcome				
0-1 years	57	62	0.83 (0.57 to 1.20)	0.323
0-2 years	120	109	0.97 (0.75 to 1.26)	0.823
0-3 years	269	193	0.94 (0.78 to 1.14)	0.538
0-4 years	350	256	0.93 (0.79 to 1.10)	0.378
0-5 years	428	367	0.87 (0.76 to 1.00)	0.042
Primary nerve outcome				
0-1 years	851	824	1.02 (0.93 to 1.13)	0.642
0-2 years	1736	1759	0.98 (0.92 to 1.05)	0.520
0-3 years	2661	2526	0.98 (0.93 to 1.03)	0.447
0-4 years	3310	3148	0.98 (0.88 to 1.09)	0.738
0-5 years	3881	3717	0.98 (0.87 to 1.09)	0.679

Captions for Figures

Figure 1. Effects of more versus less intensive glucose control on kidney events, eye events and nerve events. Horizontal lines show the 95% confidence intervals with the point estimate at the centre of the corresponding box. Boxes are proportional in size to the amount of information from each study, within each sub-plot. The summary diamonds are centred on the pooled estimates, and their width spans the corresponding 95% confidence interval.

Figure 2. Effects of more versus less intensive glucose control on kidney events. A: primary kidney outcome, its components and microalbuminuria; B: regression of albuminuria. For conventions see Figure 1.

Figure 3. Effects of more versus less intensive glucose control on eye events. For conventions see Figure 1.

Supplementary Figure 1. Effects of more versus less intensive glucose control on nerve events. For conventions see Figure 1.