

Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial



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Summary

Background Hyperglycaemia is associated with increased risk of cardiovascular complications in people with type 2 diabetes. We investigated whether reduction of blood glucose concentration decreases the rate of microvascular complications in people with type 2 diabetes.

Methods ACCORD was a parallel-group, randomised trial done in 77 clinical sites in North America. People with diabetes, high HbA_{1c} concentrations (>7·5%), and cardiovascular disease (or ≥2 cardiovascular risk factors) were randomly assigned by central randomisation to intensive (target haemoglobin A_{1c} [HbA_{1c}] of <6·0%) or standard (7·0–7·9%) glycaemic therapy. In this analysis, the prespecified composite outcomes were: dialysis or renal transplantation, high serum creatinine (>291·7 μmol/L), or retinal photocoagulation or vitrectomy (first composite outcome); or peripheral neuropathy plus the first composite outcome (second composite outcome). 13 prespecified secondary measures of kidney, eye, and peripheral nerve function were also assessed. Investigators and participants were aware of treatment group assignment. Analysis was done for all patients who were assessed for microvascular outcomes, on the basis of treatment assignment, irrespective of treatments received or compliance to therapies. ACCORD is registered with ClinicalTrials.gov, number NCT00000620.

Findings 10 251 patients were randomly assigned, 5128 to the intensive glycaemia control group and 5123 to standard group. Intensive therapy was stopped before study end because of higher mortality in that group, and patients were transitioned to standard therapy. At transition, the first composite outcome was recorded in 443 of 5107 patients in the intensive group versus 444 of 5108 in the standard group (HR 1·00, 95% CI 0·88–1·14; p=1·00), and the second composite outcome was noted in 1591 of 5107 versus 1659 of 5108 (0·96, 0·89–1·02; p=0·19). Results were similar at study end (first composite outcome 556 of 5119 vs 586 of 5115 [HR 0·95, 95% CI 0·85–1·07, p=0·42]; and second 1956 of 5119 vs 2046 of 5115, respectively [0·95, 0·89–1·01, p=0·12]). Intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, but delayed the onset of albuminuria and some measures of eye complications and neuropathy. Seven secondary measures at study end favoured intensive therapy (p<0·05).

Interpretation Microvascular benefits of intensive therapy should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycaemia.

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Introduction

Epidemiological studies of type 2 diabetes have shown that high blood glucose concentrations, as established by measurement of haemoglobin A_{1c} (HbA_{1c}) concentration, are associated with an increased risk of diabetic retinopathy, nephropathy, and neuropathy.^{1–6} Results of several clinical trials aimed at reducing HbA_{1c} concentrations have shown that intensive glycaemic control in patients with type 2 diabetes is associated with a reduction in microvascular complications (mostly in albuminuria).^{7–10}

The glycaemia arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial¹¹ was an investigation of the effects on cardiovascular events of intensive versus standard glycaemia control therapy for

hyperglycaemia in a large population with type 2 diabetes.¹² Besides the primary composite cardiovascular endpoint, the ACCORD trial had predefined secondary endpoints to assess the effect of intensive glycaemia therapy on incidence and progression of retinopathy, nephropathy, and neuropathy.

ACCORD targeted near-normal glycaemia in people with longstanding type 2 diabetes (mean 10 years) and cardiovascular disease or high cardiovascular risk. The intensive therapy aimed to reduce HbA_{1c} values to less than 6·0%, whereas the standard therapy sought to keep values between 7·0% and 7·9%, with a mean of 7·5%.¹¹ As reported,¹¹ HbA_{1c} concentrations achieved with the intensive therapy were much lower than those achieved in

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UKPDS⁷ and VADT,¹³ and were similar to those in the ADVANCE trial,⁹ which reported results from people with a similar duration of diabetes as in ACCORD. HbA_{1c} concentrations in the standard treatment group in ACCORD were lower than those achieved in UKPDS and VADT, and were similar to those reported in ADVANCE. For participants with surveillance for one or more microvascular outcomes, the intensive glycaemia control was stopped in February, 2008, after a median of 3.7 years (IQR 2.7–4.3) of follow-up because of an increase in all-cause mortality.¹⁴ However, these participants continued in the trial with the standard therapy for the planned remainder of the median 5.0 years (4.2–5.7) of follow-up to June, 2009.

Here, we report results of predefined secondary microvascular outcomes at transition of patients from intensive to standard therapy, and at the end of the full duration of the trial. The effect of glycaemia control strategies on diabetic retinopathy including fundus photography in a subset of patients is the protocol-defined main microvascular endpoint in ACCORD, and is published separately as the ACCORD-EYE study.¹⁵

Methods

Study design and participants

We recruited volunteers who had type 2 diabetes mellitus, HbA_{1c} concentrations of 7.5% or more, and were aged 40–79 years with history of cardiovascular disease or 55–79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidaemia, hypertension, being a smoker, or obesity). Exclusion criteria included frequent or recent serious hypoglycaemic events, unwillingness to monitor glucose at home or inject insulin, body-mass index of more than 45 kg/m², serum creatinine more than 132.6 µmol/L, or other serious illness. Participants were recruited at 77 clinical centres (aggregated within seven networks) in the USA and Canada. Ethics committees at every institution approved the protocol and the written informed consent forms.

ACCORD was a double two-by-two factorial, parallel treatment trial (figure 1) in which patients were randomly assigned to receive one of two glycaemia control strategies: intensive treatment targeting a HbA_{1c} concentration of less than 6.0% or standard treatment targeting HbA_{1c} of 7.0–7.9%. Patients were also assigned to one of two blood pressure interventions (intensive blood pressure target <120 mm Hg, or standard <140 mm Hg), or a lipid intervention (fenofibrate or placebo while maintaining good control of LDL-cholesterol with simvastatin). Recruitment was done in two stages. The vanguard phase recruitment was between January, 2001, and May, 2001, and treatment and follow-up was done until February, 2003; recruitment of participants in the main trial phase was between March, 2003, and October, 2005. Treatment and follow-up of all

Glycaemia trial	Blood pressure trial		Lipid trial		
	SBP<120 mm Hg	SBP<140 mm Hg	Fibrate	Placebo	
HbA _{1c} <6.0%	1178	1193	1374	1383	5128
HbA _{1c} 7.0–7.9%	1184	1178	1391	1370	5123
	2362	2371	2765	2753	
	4733		5518		10251

Figure 1: Participant randomisation strategy in the ACCORD glycaemia, blood pressure, and lipid trials
 ACCORD=Action to Control Cardiovascular Risk in Diabetes.
 HbA_{1c}=haemoglobin A_{1c}, SBP=systolic blood pressure.

participants was done until June, 2009. Participants were given instructional materials and behavioural counselling as part of their glycaemic intervention, and were provided with glucose-lowering drugs and self-monitoring supplies. Treatment regimens were individualised by study investigators (with feedback from patients) on the basis of randomised assignment and response to therapy. Adverse effects were monitored both locally and centrally to ensure participant safety.¹¹

Prespecified microvascular outcomes in ACCORD were measures of kidney function, diabetic eye complications, and peripheral neuropathy. Two composite outcomes were prespecified (table 1). The first combined advanced kidney and eye disease and was intended to approximate the primary microvascular outcome of the UKPDS study,¹⁶ and the second added peripheral neuropathy to that outcome. Table 1 summarises the predefined ACCORD microvascular outcomes and their frequency of assessment. The primary microvascular outcome based on all ACCORD participants was predefined as the first composite endpoint (development of renal failure, or retinal photocoagulation or vitrectomy to treat diabetic retinopathy), which is characterised as advanced microvascular disease. We assessed individual components of the microvascular outcomes with the standard procedures described in webappendix pp 1–2.

Randomisation and masking

Randomisation in the vanguard phase was stratified by clinical centre network and baseline cardiovascular disease status (either primary or secondary prevention) with permuted blocks of four, eight, or 12 patients. In the main trial, randomisation was stratified only by clinical site to improve balance within the 77 clinical sites with the same block sizes. Because of the improved refinement in stratification during the main trial, baseline cardiovascular disease status was dropped as a stratification factor.

Unique randomisation sequences were computer generated for every clinical site centrally at the coordinating centre. Randomisation was done by clinical staff via secure access to the ACCORD trial website. Electronic verification of inclusion and exclusion criteria was done before patients were assigned to a treatment

See Online for webappendix



Definition		Assessment frequency
Composite outcomes		
First	Development of renal failure (initiation of dialysis or ESRD, renal transplantation, or rise of serum creatinine >291.72 µmol/L), or retinal photocoagulation or vitrectomy to treat retinopathy	Every 4 months
Second	Score of >2.0 on MNSI or first composite outcome	Every 4 months
Nephropathy		
Neph-1	Development of microalbuminuria (urine albumin:creatinine ratio ≥3.4 mg/mmol)	Every year
Neph-2	Development of macroalbuminuria (urine albumin:creatinine ratio ≥33.9 mg/mmol)	Every year
Neph-3	Development of renal failure (defined as initiation of dialysis or ESRD, or renal transplantation, or rise of serum creatinine >291.72 µmol/L in absence of an acute reversible cause)	Every 4 months
Neph-4	Doubling of baseline serum creatinine or more than 20 mL/min per 1.73 m ² decrease in estimated GFR. (GFR estimation is done on the basis of the four variable MDRD GFR equation from Levey and colleagues ¹⁶)	Every 4 months
Neph-5	Development of Neph-2, Neph-3, or Neph-4	Every 4 months
Diabetic eye complications		
Eye-1	Retinal photocoagulation or vitrectomy to treat retinopathy	Every year
Eye-2	Eye surgery for cataract extraction	Every year
Eye-3	Three-line change in visual acuity (as measured using LogMAR visual acuity chart)	Every 2 years
Eye-4	Severe vision loss (Snellen fraction <20/200)	Every 2 years
Neuropathy		
Neuro-1	New score of >2.0 on MNSI	Every year
Neuro-2	New loss of vibratory sensation (tested with 128 Hz tuning fork)	Every year
Neuro-3	New loss of ankle jerk during Jendrassik manoeuvre	Every year
Neuro-4	New loss of light touch (10 g force monofilament test)	Every year
<small>ACCORD=action to control cardiovascular risk in diabetes. ESRD=end-stage renal disease. MNSI=Michigan neuropathy screening instrument. GFR=glomerular filtration rate. MDRD=modification of diet in renal disease.</small>		
Table 1: ACCORD trial microvascular outcomes and assessment frequency		

group. Glycaemia trial treatment assignment was open-label, and both clinic staff and patients were aware of glycaemic goal assigned. Study investigators were masked to results of interim analyses.

Statistical analysis

ACCORD's sample size of 10 000 was designed to have 89% power to detect a 15% treatment effect of intensive glycaemic control compared with standard glycaemic control on the primary composite outcome of cardiovascular disease—death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Descriptive statistics of a subset of continuous factors related to treatment in every trial were calculated by glycaemia treatment group at the date of transition from intensive to standard therapy for the glycaemia trial and again at study end. Differences in these factors were assessed by use of the Wilcoxon signed-rank test.

Table 1 describes microvascular events for every predefined outcome. For each patient and outcome, observation was censored at the last surveillance time if no event was recorded. If an event was reported, an event time was assigned with the midpoint between the time of event discovery and the most recent previous surveillance time.¹⁸ Interim analyses of intervention effectiveness were done every 6 months for meetings of the data safety and monitoring board. Overall type 1 error was controlled via the group sequential procedure

of Lan and DeMets.¹⁹ Two sets of analyses were done. The first assessed outcomes before transition (Feb 5, 2008), and the second assessed all outcomes until the last study visit (March–June, 2009).

The effect of the different glycaemia control therapies on time to occurrence of the first microvascular event of every type was analysed with proportional hazards regression models to estimate hazard ratios and assess statistical significance. Graphical depiction of time to event was done with Kaplan-Meier plots. The main statistical test for every outcome was taken from a model that accounted for glycaemia treatment group assignment, second trial treatment group assignment (intensive or standard blood pressure management in the blood pressure trial, or fenofibrate or placebo assignment in the lipid trial), and an indication of history of clinical cardiovascular disease at baseline as prespecified in the study protocol. The proportional hazards assumption was assessed by examination of log(-log[survival]) plots. Analysis of the plots showed that the assumption of proportional hazards was tenable.

Analyses included participants with microvascular assessment, who were analysed on the basis of treatment assignment irrespective of treatments received or compliance to therapies. No p-value correction was applied to account for multiple hypothesis tests.²⁰ Outcomes presented in this Article were prespecified and future analyses will be done to

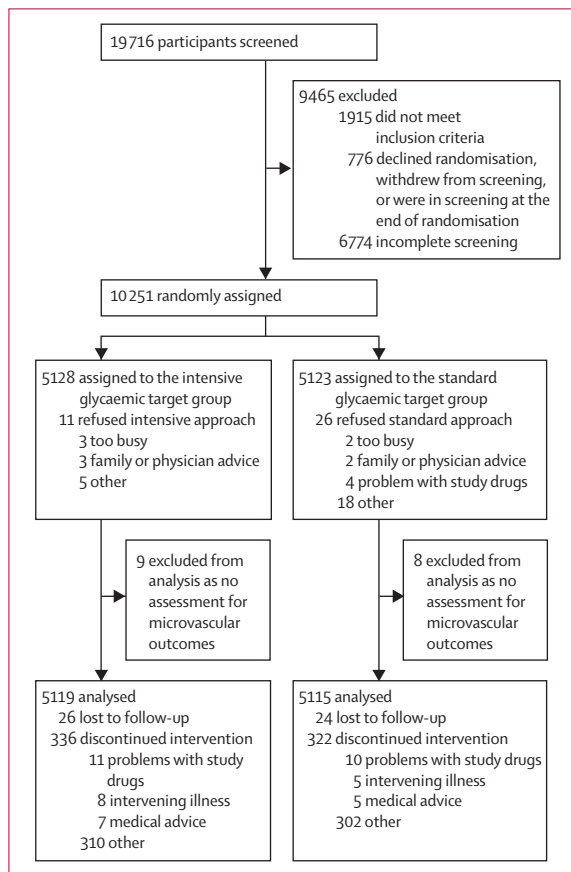


Figure 2: ACCORD trial profile
ACCORD=Action to Control Cardiovascular Risk in Diabetes.

address post-hoc hypotheses. Analyses were done with SAS version 9.2.

Role of the funding source

Staff from the National Heart, Lung, and Blood Institute (the sponsor of ACCORD) served on the Executive and Steering Committees in which decisions on study design, intervention approaches, data collection, analysis, interpretation, and review of reports were made. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

10251 participants were assigned to therapy. 1174 participants were randomly assigned in the vanguard phase with an additional 9077 randomised during the main trial. Figure 2 shows the process of screening and randomisation. Participants had a median age of 62 years (IQR 57–67), and type 2 diabetes for around 10 years. Tables 2 and 3 show continuous and categorical baseline participant characteristics by glycaemia intervention group assignment. When the ACCORD intensive glycaemia control was discontinued

(at transition to standard therapy), the two glycaemia groups differed with respect to median HbA_{1c} ($p < 0.0001$; table 4). At study end, median HbA_{1c} concentration was still significantly lower in participants who had previously been intensively managed than in those in the standard group ($p < 0.0001$). Systolic and diastolic blood pressures were significantly reduced from baseline in both groups at the time of transition, and remained so at study end (table 4). HDL concentrations were slightly higher in both men and women in the intensive group at transition compared with standard treatment. Triglyceride concentrations were 0.16 mmol/L lower in the intensive target group than in the standard glycaemia group at transition; and a small difference remained at study end. As previously reported,¹⁴ the intensive therapy group had a significantly higher body-mass index at transition than did the standard group, and the difference remained at study end. Serum creatinine concentrations were not different between the two groups at transition or at study end. The median ratio of albumin to creatinine was significantly lower in the intensive group than it was in the standard group at both transition and study end (table 4).

The primary composite outcome of advanced nephropathy and diabetic eye complications (table 1) did not differ between groups at transition (figures 3 and 4) or at study end (figure 5). The second composite endpoint, which added a peripheral neuropathy outcome to the primary composite outcome, also did not differ at transition (figure 4) or at study end (figure 5).

Microvascular renal outcomes based on urinary measurements were significantly reduced in the intensive glycaemia group. Intensive glycaemia therapy led to a 21% reduction in development of microalbuminuria at transition (figure 4); this effect was attenuated (15%) but remained significant at study end (figure 5). Incidence of macroalbuminuria was reduced in the intensive group compared with the standard group at transition and at study end (figures 4 and 5). The number of patients with overt renal failure was alike in both groups at study end (figure 5). There was a significant difference between the groups at transition in the microvascular renal outcome based on serum creatinine or estimated glomerular filtration rate (eGFR) that favoured the standard glycaemia group (figure 4); although the difference was not significant at study end. The difference between treatment groups in this renal outcome was attributable to a decline in eGFR in the intensive group in the first 24 months, possibly because of a decrease in glomerular hyperfiltration associated with improved glycaemic control (figure 6); serum creatinine and eGFR concentrations remained within the normal range. A composite of prespecified renal outcomes—not including incident microalbuminuria—did not differ between groups at transition or study end (Neph-5 outcome; figures 4 and 5). At study end, there was no difference in microvascular renal outcomes

	Intensive glycaemia control		Standard glycaemia control	
	n	Median (IQR)	n	Median (IQR)
HbA _{1c} (%)	5101	8.1% (7.6–8.9%)	5111	8.1% (7.6–8.9%)
Fasting serum glucose (mmol/L)	5080	9.33 (7.71–11.32)	5090	9.27 (7.66–11.32)
Systolic blood pressure (mm Hg)	5095	135 (125–147)	5094	135 (125–147)
Diastolic blood pressure (mm Hg)	5095	75 (68–82)	5094	75 (68–82)
LDL cholesterol (mmol/L)	5082	2.59 (2.10–3.24)	5093	2.61 (2.10–3.24)
HDL cholesterol in women (mmol/L)	1953	1.16 (0.98–1.37)	1969	1.16 (0.98–1.40)
HDL cholesterol in men (mmol/L)	3129	0.96 (0.83–1.14)	3124	0.96 (0.83–1.11)
Triglycerides (mmol/L)	5082	1.74 (1.22–2.55)	5093	1.76 (1.19–2.60)
Body-mass index (kg/m ²)	5112	31.7 (28.2–35.9)	5116	31.9 (28.1–35.9)
Serum creatinine (μmol/L)	5093	79.6 (70.7–88.4)	5081	79.6 (70.7–88.4)
eGFR (mL/min per 1.73 m ²)	5093	90 (76–105)	5081	90 (75–105)
Urine albumin:creatinine ratio (mg/mmol)	5083	1.54 (0.78–5.04)	5071	1.54 (0.77–4.95)
Average right/left eye visual acuity score	4874	77 (69–82)	4908	77 (69–82)
Average right/left eye Snellen fraction	4933	32 (25–44)	4961	32 (25–42)
MNSI score	4997	2.0 (0.5–3.0)	4990	2.0 (0.5–3.0)

HbA_{1c}=haemoglobin A_{1c}; eGFR=estimated glomerular filtration rate. MNSI=Michigan neuropathy screening instrument.

Table 2: Continuous factor covariates and components of microvascular outcomes at baseline, by glycaemia trial group

between groups, apart from microalbuminuria and macroalbuminuria (figure 5).

For diabetes-related eye events, three-line worsening of visual acuity was more common in the standard group than in the intensive group at transition and at study end (figures 4 and 5). Cataract extraction was also significantly reduced (by 21%) in the intensive group compared with standard group at study end (figure 5). Other diabetes-related eye outcomes did not differ significantly between the two groups.

Peripheral neuropathy, as established by a Michigan neuropathy screening instrument score of 2.0 or more, was less common in the intensive group than in the standard therapy group at study end (figure 5). Loss of ankle jerk reflex and light touch (10 g monofilament) perception were both rarer in the intensive than in the standard therapy at study end (figure 5); light touch was also reduced at transition (figure 4). Loss of vibratory sensation did not differ significantly between the two groups. The webappendix contains Kaplan-Meier plots of all secondary microvascular outcomes.

Discussion

We recorded no significant effect of intensive glycaemia therapy on the two prespecified composite microvascular outcomes—1) advanced renal or eye complications, or 2) these two outcomes or peripheral neuropathy.

Microvascular complications including nephropathy, retinopathy, and neuropathy are an important source of morbidity in patients with type 2 diabetes. Analysis of available epidemiological evidence suggests that hyperglycaemia is an important contributor to development and progression of microvascular complications in type 2 diabetes.⁶ Although some clinical trials^{4,7,8} reported a

	Intensive glycaemia control	Standard glycaemia control
	Frequency/n (%)	Frequency/n (%)
Macroalbuminuria	339/5071 (7%)	327/5083 (6%)
Microalbuminuria	1241/4732 (26%)	1264/4756 (27%)
History of photocoagulation or vitrectomy	466/5090 (9%)	428/5106 (8%)
History of cataract removal	576/5091 (11%)	574/5107 (11%)
Number of eyes with blindness		
One	139/5023 (3%)	129/5014 (3%)
Two	16/5023 (<1%)	15/5014 (<1%)
MNSI score >2.0	2185/5095 (43%)	2160/5106 (42%)
Vibratory sensation loss	694/5070 (14%)	683/5076 (13%)
Ankle jerk loss	1648/5049 (33%)	1599/5053 (32%)
Loss of light touch	330/5075 (7%)	300/5081 (6%)

MNSI=Michigan neuropathy screening instrument.

Table 3: Categorical factor covariates and components of microvascular outcomes at baseline, by glycaemia trial group

decrease in occurrence of microvascular endpoints with lowering of HbA_{1c}, findings from recent trials^{9,13} showed less benefit in elderly patients or those with long-term diabetes than in younger patients or those with short-duration disease.

Results of the UKPDS⁷ showed a decrease with intensive treatment in the composite retinal-renal outcome used by ACCORD, with a smaller reduction in HbA_{1c} than was attained in ACCORD. However, the UKPDS cohort was younger than in ACCORD, was studied from the time of diagnosis of diabetes, and was treated intensively for 11 years, albeit with a higher HbA_{1c} concentration than was achieved in ACCORD.⁷

Analysis of secondary renal endpoints shows that the risk of development of macroalbuminuria was 29%



	At transition to standard therapy (February, 2008)*					End of study (June, 2009)				
	Intensive glycaemia control		Standard glycaemia control		p value	Intensive glycaemia control		Standard glycaemia control		p value
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
HbA _{1c} concentration (%)	4517	6.3% (5.9–7.0%)	4577	7.6% (7.0–8.2%)	<0.0001	4404	7.2% (6.6–7.9%)	4437	7.6% (7.0–8.3%)	<0.0001
Fasting serum glucose	4232	5.88 (4.94–7.33)	4292	8.16 (6.66–9.93)	<0.0001	4352	7.38 (6.05–9.05)	4385	8.21 (6.60–9.93)	<0.0001
Systolic blood pressure (mm Hg)	4524	127 (116–138)	4583	128 (116–139)	0.0144	4417	128 (117–139)	4444	128 (117–138)	0.0554
Diastolic blood pressure (mm Hg)	4524	67 (60–74)	4583	68 (61–75)	0.0003	4417	68 (61–75)	4444	67 (61–74)	0.0070
Total cholesterol	4245	4.03 (3.52–4.74)	4316	4.09 (3.52–4.79)	0.1206	4355	4.01 (3.50–4.77)	4390	4.07 (3.50–4.77)	0.2613
LDL cholesterol	4244	2.17 (1.74–2.69)	4315	2.15 (1.71–2.67)	0.1955	4355	2.09 (1.68–2.69)	4390	2.12 (1.68–2.67)	0.8305
HDL cholesterol in women	1634	1.22 (1.04–1.45)	1633	1.19 (1.01–1.40)	0.0050	1674	1.24 (1.04–1.48)	1676	1.22 (1.04–1.45)	0.2820
HDL cholesterol in men	2610	1.01 (0.85–1.22)	2682	0.98 (0.83–1.17)	0.0014	2681	1.01 (0.85–1.19)	2714	1.01 (0.85–1.19)	0.6150
Triglycerides	4245	1.43 (1.01–2.10)	4316	1.59 (1.11–2.36)	<0.0001	4355	1.48 (1.03–2.16)	4390	1.53 (1.08–2.24)	0.0003
Body-mass index (kg/m ²)	3768	33 (29–37)	3789	32 (28–36)	<0.0001	4061	33 (29–37)	4067	32 (28–36)	<0.0001
Serum creatinine (μmol/L)	4395	87.5 (73.4–107.0)	4466	87.5 (72.5–107.0)	0.9612	4381	86.6 (71.6–106.1)	4420	87.5 (71.6–108.7)	0.1950
Urine albumin:creatinine ratio (mg/mmol)	4297	1.19 (0.64–3.42)	4380	1.36 (0.7–4.47)	<0.0001	4176	1.44 (0.72–5.20)	4244	1.63 (0.77–6.33)	<0.0001

Data are mmol/L unless otherwise stated. *Data restricted to measurements within 1 year of transition date apart from urine albumin:creatinine ratio, which was within 2 years of transition. HbA_{1c}=haemoglobin A_{1c}.

Table 4: Patient characteristics at transition to standard glycaemic therapy and at end of study, by glycaemia treatment group assignment

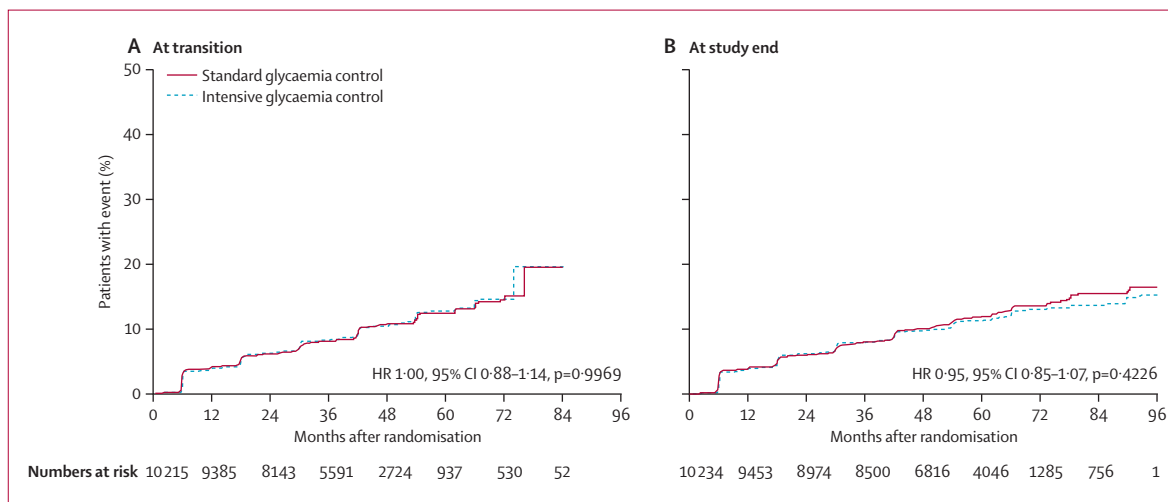


Figure 3: Kaplan-Meier plots of the microvascular primary composite outcome, by glycaemia group

The outcome was defined as development of renal failure, retinal photocoagulation, or vitrectomy to treat retinopathy. (A) Data until transition of intensive glycaemia group to standard therapy. (B) All data until end of study. Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment group assignment.



lower with intensive therapy both at transition and at study end than with standard therapy. Macroalbuminuria is a known risk factor for renal insufficiency²¹ and cardiovascular disease.²² We noted reductions in albuminuria with intensive glycaemia therapy similar to those in the ADVANCE⁹ and VADT¹³ trials. Collectively, these findings emphasise the benefits of glycaemic control for reduction of albuminuria in an important group of patients with type 2 diabetes (ie, elderly patients, and those with long-term disease or with established cardiovascular disease or high cardiovascular risk). The increase noted in the composite outcome of doubling of serum creatinine or a 20 mL/min or more decrease in eGFR with intensive therapy was largely

attributable to a slight and transient differential increase in serum creatinine in the intensive group during the first 2 years of the trial. Mean serum creatinine concentrations at baseline, transition, and end of study were similar in the two treatment groups (tables 2–4).

By contrast with UKPDS,⁷ we did not record a clear benefit of intensive therapy for diabetic retinopathy on the basis of major clinical endpoints (such as necessity of photocoagulation); our result is consistent with VADT⁹ and ADVANCE.¹³

The significant reductions in the development of peripheral neuropathy, if further sustained, suggest that intensive glycaemia therapy could decrease the risk of ulcers and number of future leg amputations.²³

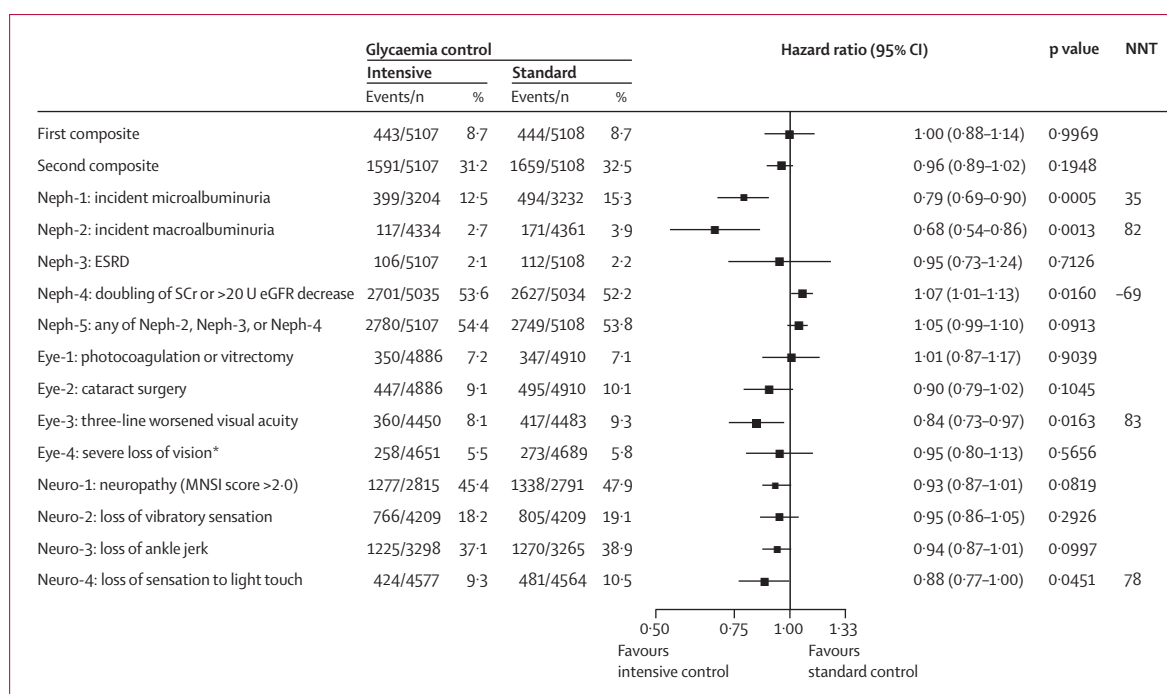


Figure 4: Comparison of intensive and standard glycaemic therapy for all microvascular outcomes, until transition

Intensive therapy was stopped before study end because of increased mortality, and patients were transitioned to standard therapy. Hazard ratios adjusted for baseline clinical cardiovascular disease history and second trial treatment group assignment. NNT=number needed to treat. ESRD=endstage renal disease (defined as requirement of dialysis or serum creatinine concentration of more than 291.72 μmol/L). SCr=serum creatinine. eGFR=estimated glomerular filtration rate. MNSI=Michigan neuropathy screening instrument score. *Defined as Snellen fraction <20/200.

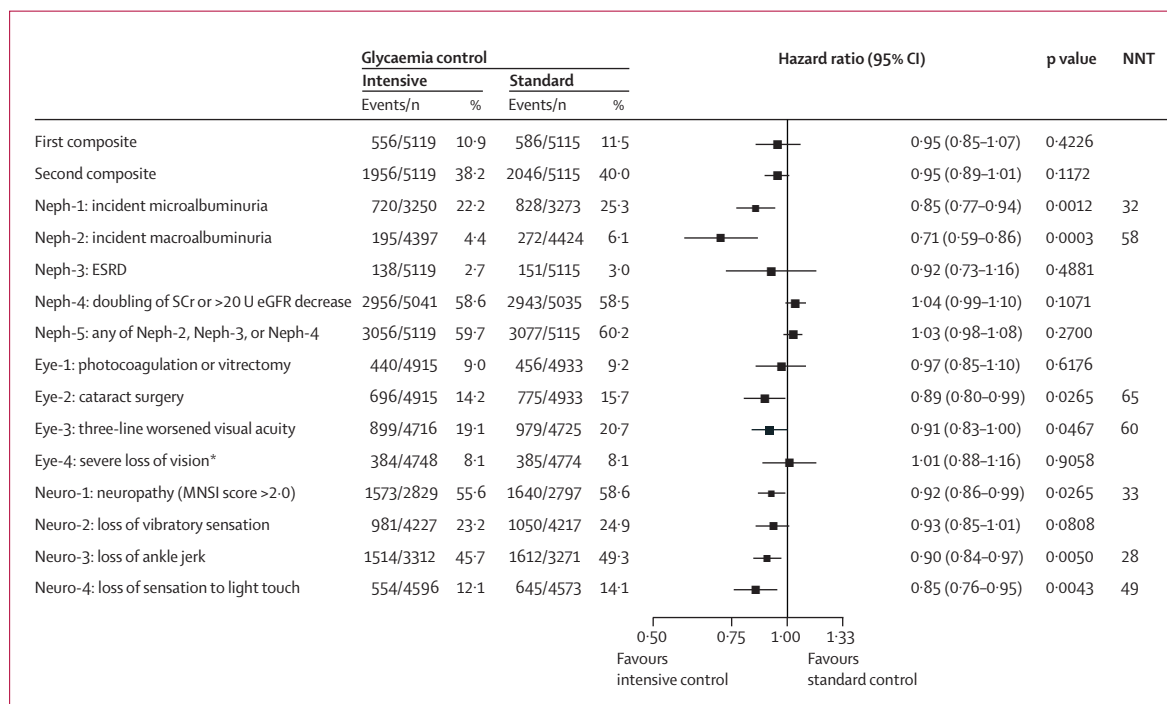


Figure 5: Comparison of intensive and standard glycaemic therapy for all microvascular outcomes, until end of study

Intensive therapy was stopped before study end because of increased mortality, and patients were transitioned to standard therapy. Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment group assignment. NNT=number needed to treat. ESRD=endstage renal disease (defined as requirement of dialysis or serum creatinine concentration of more than 291.72 μmol/L). SCr=serum creatinine. eGFR=estimated glomerular filtration rate. MNSI=Michigan neuropathy screening instrument score. *Defined as Snellen fraction <20/200.

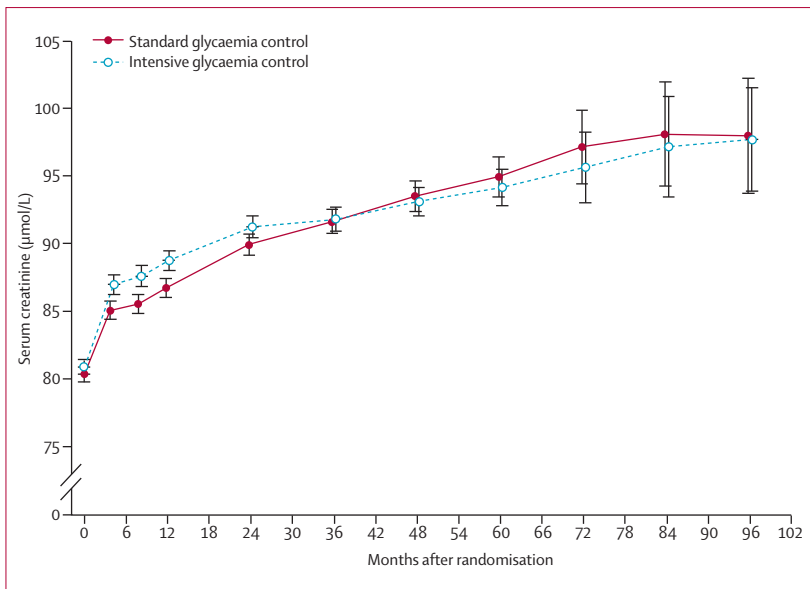


Figure 6: Mean serum creatinine levels at follow-up in intensive and standard glycaemic therapy groups. Vertical lines show \pm two standard errors of the mean.

The beneficial effects of intensive therapy on surrogate secondary microvascular outcomes compared with standard therapy should be balanced against observed risks. The 22% relative and 0.27% per year absolute increase in all-cause mortality recorded with intensive glycaemia therapy in ACCORD prompted the discontinuation of intensive glycaemia control and transition of patients to standard glycaemia therapy.¹⁴ Additionally, intensive therapy led to increased body-mass index and a three-fold increase in frequency of severe hypoglycaemia.¹⁵ Furthermore, no overall cardiovascular disease benefit had accrued, although non-fatal myocardial infarction was reduced by 24% ($p=0.004$).¹⁴ In subgroup analysis, there was a reduction in the primary composite cardiovascular disease outcome (but not in total mortality) in patients who entered the study with no previous history of cardiovascular disease events or with an HbA_{1c} of 8.0% or less.¹⁴ Overall, targeting of HbA_{1c} of 6.0% or less with the methods used for the ACCORD cohort is not recommended on the basis of the microvascular benefits associated with intensive glycaemia therapy. Any benefits should be weighed against the recorded increase in total and cardiovascular disease-related mortality, increased weight gain, and increased risk of severe hypoglycaemia in intensively-treated patients.

In this multicentre trial, we tried to adhere to the intention-to-treat principle for analysis of data from baseline to transition, and from baseline to study end, analysing all participants who were assessed for microvascular outcomes. The significant difference noted in the mean HbA_{1c} concentration of the two originally randomised treatment groups persisted from transition to the end of the study. The differences in HbA_{1c} during

follow-up exceeded those reported by the UKPDS⁷ and ADVANCE,⁹ but was less than that achieved in VADT.¹³ Loss to follow-up were very low.

One limitation was that investigators were not masked to treatment strategies or outcomes. Another was that follow-up might have been too short to show effects of treatment on some endpoints. In UKPDS, cardiovascular and microvascular benefits persisted or became increasingly evident after 10 years. Although not generally accepted,²⁴ a post-hoc power analysis for the primary composite outcome in our study showed 66% power to detect a 15% risk reduction in the intensive glycaemia group at transition, and 82% at the end of the investigation. A similar analysis for the second composite outcome showed powers of 87% to detect a 10% risk reduction at transition and 92% at end of study. Another limitation was that the ratio of albumin to creatinine instead of a timed albumin excretion rate was measured in ACCORD. However, good correlation between the two measures of albumin excretion rate has been noted,^{25,26} although variable intraindividual correlation²⁷ and regression of the albumin to creatinine ratio to normal has also been reported.^{28–30} Furthermore, the eGFR is not validated as an accurate measure of changes in glomerular filtration rate in patients without significant renal disease. Although ACCORD investigators were trained centrally to do tests for neuropathy, they were not certified for the procedure.

Analytical limitations included the use of midpoint interval imputation for calculation of survival times in outcomes for which time of event was unknown. Surveillance intervals for all outcomes were less than 2 years, and some outcomes were assessed every 4 months or 12 months. Law and Brookmeyer,¹⁸ in their examination of the effect of midpoint imputation on doubly censored survival data, showed that traditional survival techniques provide an adequate approximation of survival estimates in large samples with intervals of 2 years or less. Finally, because 15 outcomes were assessed, if we had done independent tests, there would be a 54% chance (ie, $1-[1-0.05]^{15}$) of at least one type I statistical error for both transition and end of study analyses.³¹

The observed benefits associated with intensive glycaemia management should be weighed against higher total and cardiovascular-related mortality, weight gain, and severe hypoglycaemia in patients at high risk of cardiovascular disease. Hence, caution should be exercised in pursuit of a strategy of intensive glycaemic control for prevention of microvascular complications in patients with established type 2 diabetes and characteristics similar to those in the ACCORD trial. An HbA_{1c} target of 6.0% or less with present strategies seems imprudent. Long-term assessment of benefits versus risks should be done through follow-up of the ACCORD participants.

Contributors

FI-B implemented the protocol and was lead author. TC coordinated the methods section and did the statistical analysis. MAB contributed to the methods section. JB, RC, LK, US, and AT contributed to the results section. JC, RMC, BH, PO'C, RP-B, and DW contributed to the results and discussion sections. WCC and RHG contributed to the design and implementation of the protocol and to the discussion section. SG contributed to the design and implementation of the protocol, and coordinated the discussion section. BPH and AK contribution to the discussion section. DK coordinated the introduction section. DS contributed to the methods, results, and discussion sections. HT contributed to the methods and discussion sections. IH coordinated the results section. All authors approved the final report.

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