

Durable change in glycaemic control following intensive management of type 2 diabetes in the ACCORD clinical trial

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Abstract

Aims/hypothesis We aimed to determine the persistence of glycaemic control 1 year after a limited period of intensive glycaemic management of type 2 diabetes.

Methods 4119 ACCORD Trial participants randomised to target HbA_{1c} <6.0% (42 mmol/mol) for 4.0±1.2 years were systematically transitioned to target HbA_{1c} 7.0–7.9% (53–63 mmol/mol) and followed for an additional 1.1±0.2 years. Characteristics of participants with HbA_{1c} <6.5% (48 mmol/mol) or ≥6.5% at transition were compared. Changes in BMI and glucose-lowering

medications were compared between those ending with HbA_{1c} <6.5% vs ≥6.5%. Poisson models were used to assess the independent effect of attaining HbA_{1c} <6.5% before transition on ending with HbA_{1c} <6.5%.

Results Participants with pre-transition HbA_{1c} <6.5% were older with shorter duration diabetes and took less insulin but more non-insulin glucose-lowering agents than those with higher HbA_{1c}. A total of 823 participants achieved a final HbA_{1c} <6.5%, and had greater post-transition reductions in BMI, insulin dose and secretagogue and acarbose use than those with higher HbA_{1c} ($p<0.0001$). HbA_{1c} <6.5% at

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transition predicted final HbA_{1c} <6.5% (crude RR 4.9 [95% CI 4.0, 5.9]; RR 3.9 [95% CI 3.2, 4.8] adjusted for demographics, co-interventions, pre-intervention HbA_{1c}, BMI and glucose-lowering medication, and post-transition change in both BMI and glucose-lowering medication). Progressively lower pre-transition HbA_{1c} levels were associated with a greater likelihood of maintaining a final HbA_{1c} of <6.5%. Follow-up duration was not associated with post-transition rise in HbA_{1c}.

Conclusions/interpretation Time-limited intensive glycaemic management using a combination of agents that achieves HbA_{1c} levels below 6.5% in established diabetes is associated with glycaemic control more than 1 year after therapy is relaxed.

Keywords Intensive glucose lowering · Long-term glycaemic control · Post-intervention follow-up · Type 2 diabetes

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
CDE	Certified diabetes educator
SMBG	Self-monitoring of blood glucose

Introduction

Type 2 diabetes is generally regarded as a slowly progressive disease characterised by a reduction in ability to maintain glucose homeostasis over time [1] and a concomitant increase in the need for pharmacological therapy to do so. Recent observations that bariatric surgery seems to slow or even reverse this process [2, 3] suggest that diabetes is not necessarily progressive and that beta cell function and the capacity to make insulin can be improved [4, 5] in association with reduced body mass and food intake. Additional evidence suggests that short-term intensive insulin therapy early in the course of diabetes [6] plus lifestyle modification [7] may have persistent effects on glycaemic control by reducing the demand on the beta cells to secrete insulin, thereby preserving their function [8, 9], or by improving adherence to health-promoting behaviours. Other agents, including thiazolidinediones and incretin mimetics, also improve beta cell function [8, 9]. It is not known whether a strategy of prolonged multimodal intensive glucose lowering has durable effects.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial (NCT00000620) was designed to study the cardiovascular effects of intensive glycaemic control, intensive blood pressure control, and fibrate use among people with type 2 diabetes. As previously reported [10], the

intensive glycaemic intervention was discontinued after the independent data and safety monitoring board noted excess mortality in that group. As a result, participants who had been randomised to intensive glycaemic management (i.e. targeting an HbA_{1c} of <6.0% [42 mmol/mol]) and who, as a group, had reduced their entry median HbA_{1c} from 8.1% (65 mmol/mol) to 6.4% (46 mmol/mol) were all transitioned to the standard glycaemic management strategy (i.e. targeting an HbA_{1c} of 7.0–7.9% [53–63 mmol/mol]), and continued to be followed until the blood pressure and lipid trials that were part of the initial ACCORD design were completed about 1 year later. By the end of the follow-up period, the HbA_{1c} in this group was 7.4±1.2% compared with 7.8±1.2% in the group randomised to standard care [11]. This situation offered a unique opportunity to observe the glycaemic effects of intentional relaxation of glycaemic therapy in a group of patients who started out with poorly controlled (HbA_{1c} >7.5% [58 mmol/mol]), longstanding (median 10 years) type 2 diabetes, and who achieved near-normal HbA_{1c} levels during more than 3 years of intensive glucose lowering. This report therefore describes the metabolic course of participants randomised to the intensive glycaemia group who had at least one visit before transition and one visit after transition to a standard glycaemic management approach, and determines whether a period of intensive glucose lowering that achieved normal or near-normal glucose levels is associated with persistence of glycaemic control after relaxation of therapy.

Methods

ACCORD Trial The design of the ACCORD Trial has been described previously [12, 13]. Briefly, 10,251 participants aged 40–79 years with type 2 diabetes, an HbA_{1c} ≥7.5% and additional cardiovascular risk factors were recruited at 77 sites in North America. Participants were randomised to either intensive glycaemic management targeting an HbA_{1c} of <6.0% or standard glycaemic management targeting an HbA_{1c} of 7.0–7.9%. In a double 2×2 factorial design, 4,733 participants were also randomised to either intensive blood pressure lowering (<120/80 mmHg) or standard blood pressure lowering (130–139/80–90 mmHg), and the remaining 5,518 participants were randomised to the addition of fenofibrate or placebo to statin therapy. The trial was approved by ethics committees at all participating sites, and all participants gave informed consent.

The intensive glycaemic management strategy targeting an HbA_{1c} of <6.0% involved monthly visits for the first 4 months followed by visits every 1–2 months, which included review of logs of self-monitoring of blood glucose (SMBG; performed two to eight times per day) and point-of-care HbA_{1c} (every 2 months), review and prescription or titration of glucose-lowering medication from all approved classes in

any combination to further lower HbA_{1c} if it could be achieved safely while avoiding hypoglycaemia, and education regarding diabetes self-management including diet, physical activity, insulin self-titration, hypoglycaemia avoidance and management, with additional supportive phone calls between visits.

The standard management strategy targeting an HbA_{1c} of 7.0–7.9% included visits every 4 months (except for participants also randomised to intensive blood pressure control, who had visits every 2 months) to review logs of SMBG (performed a few times per week to three times per day), education regarding diabetes self-management as needed, and review and prescription or titration of glucose-lowering medication including down-titration for any of the following reasons: severe or frequent symptomatic hypoglycaemia; 50% or more SMBG values below 5 mmol/l (90 mg/dl); or in the setting of either one HbA_{1c} <6.5% or consecutive HbA_{1c} values <7.0%, any of use of insulin or a secretagogue, any symptomatic hypoglycaemia or any SMBG below 5 mmol/l (90 mg/dl).

An extra visit was scheduled for all intensive group participants at the time of the transition to explain the new HbA_{1c} goal of 7.0–7.9%, and their conversion to the standard management strategy of the trial as described above. At this transition visit, research staff reviewed SMBG values, point-of-care HbA_{1c} and medications, and down-titrated medications for individuals with an HbA_{1c} <7.0%.

Glucose-lowering medications, BMI and a centrally measured HbA_{1c} were documented prior to randomisation and at least every 4 months for all participants throughout the study. Glycaemic status of all participants was reviewed centrally and reported to investigators regularly to promote adherence to the standard glycaemic management strategy after transition. In particular, site investigators were sent regular reminders of the down-titration algorithm, reports indicating the proportion of formerly intensive group participants at their site whose medications were down-titrated according to the standard management algorithm, and listings of intensive group participants whose HbA_{1c} remained <7.0%. Extra visits or phone calls were completed to further down-titrate glucose-lowering medications as needed to achieve an HbA_{1c} of 7.0–7.9%.

The last study visit on or before the date of the transition at which HbA_{1c} was measured centrally was considered the pre-transition visit, and pre-transition values were obtained from that visit. Thereafter, the last study visit at which HbA_{1c} was measured centrally was considered the final post-transition visit, and post-transition values were obtained from that visit.

Participants All participants allocated to the intensive group who were alive at the time of transition and who had at least one HbA_{1c} measurement at or before the date of transition and at least one measurement after the transition date were included in this analysis.

Statistical methods All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC, USA). Two-sided *p* values <0.05 were considered nominally significant. Before any analyses were conducted, a decision was made to assess the effect of achieving a pre-transition HbA_{1c} <6.5% on the final HbA_{1c} level. This threshold was chosen because it was just above the median HbA_{1c} level achieved in the intensive group during the ACCORD Trial (i.e. 6.4%) and thus represented approximately half of the intensive group participants. It is also the threshold used to diagnose diabetes [14].

Characteristics of intensive group participants whose last pre-transition HbA_{1c} was <6.5% vs ≥6.5% were compared by *t* tests or χ^2 tests. Mean insulin doses were calculated based on all participants; those not on insulin were assigned a dose of 0 units for the analyses. Participants whose final post-transition HbA_{1c} was <6.5% vs ≥6.5% were compared for mean final HbA_{1c}, post-transition change in BMI (three categories), change in insulin dose (three categories), and change in use of other glucose-lowering medications (added, continued, never prescribed or discontinued for each medication class) by χ^2 tests.

RRs with 95% CI of achieving a final post-transition HbA_{1c} <6.5% were calculated for a pre-transition HbA_{1c} <6.5% vs ≥6.5% using Poisson regression, both before and after adjustment for baseline pre-randomisation HbA_{1c} and demographic, anthropometric, co-interventional and pharmacological covariates listed in Tables 1 and 2. To assess the relationship between the pre-transition and final HbA_{1c} levels, RRs were calculated for 0.1% increments of the pre-transition HbA_{1c} level. Comparisons were relative to those who had a pre-transition HbA_{1c} equal to 6.5% using unadjusted and adjusted Poisson regression. Lines were fitted assuming a single linear term for pre-transition HbA_{1c} in a log-linear model. Finally, to determine if HbA_{1c} levels ‘drifted’ up with a greater duration of exposure to the standard glycaemic intervention after transition, a second degree penalised B-spline was fitted for change in HbA_{1c} vs time between pre-transition and final HbA_{1c} measurements [15].

Results

A total of 4,119 participants who were allocated to intensive glycaemic management and who had at least one HbA_{1c} level measured before and after transition to the approach used in the standard glycaemic group were analysed. Excluded intensive group participant characteristics are summarised in the electronic supplementary material (ESM) Table 1 for comparison. The mean ± SD duration of intensive glycaemic management in the pre-transition period was 4.0±1.2 years (range 2.3–7.0). As noted in Table 1, compared with the 1,786 intensive group participants whose HbA_{1c} before transition

Table 1 Baseline and pre-transition characteristics of intensive group participants who were transitioned to standard care and followed-up after transition

Characteristic	Last HbA _{1c} before transition <6.5% (<i>n</i> =2,333 ^a)	Last HbA _{1c} before transition ≥6.5% (<i>n</i> =1,786 ^a)	<i>p</i> value
Female	843 (36.1)	732 (41.0)	0.002
Randomised to receive fibrates	628 (26.9)	475 (26.6)	0.8
Randomised to intensive BP control	511 (21.9)	410 (23.0)	0.4
CDE availability at site	976 (41.8)	662 (37.1)	0.002
At randomisation			
HbA _{1c} (%)	8.1±1.0	8.5±1.0	<0.0001
HbA _{1c} (mmol/mol)	65±11	69±11	<0.0001
BMI (kg/m ²)	32.4±5.4	32.0±5.5	0.009
Insulin use	600 (25.7)	791 (44.3)	<0.0001
Metformin use	1,407 (60.3)	1,099 (61.5)	0.4
Thiazolidinedione use	444 (19.0)	372 (20.8)	0.2
Sulfonylurea use	1,257 (53.9)	861 (48.2)	0.0003
Meglitinide use	47 (2.0)	37 (2.1)	0.9
α-Glucosidase inhibitor use	9 (0.4)	20 (1.1)	0.005
At transition			
Age (years)	66.1±6.6	65.3±7.0	<0.0001
Diabetes duration (years)	13.5±7.6	15.8±8.0	<0.0001
HbA _{1c} (%)	5.9±0.3	7.3±0.9	<0.0001
HbA _{1c} (mmol/mol)	41±3	56±10	<0.0001
BMI (kg/m ²)	33.3±6.1	33.6±6.2	0.1
Total daily insulin dose (U/kg) ^b	0.4±0.4	0.7±0.6	<0.0001
Metformin use	1,900 (81.4)	1,324 (74.1)	<0.0001
Thiazolidinedione use	1,489 (63.8)	846 (47.4)	<0.0001
Secretagogue use	1,541 (66.1)	1,043 (58.4)	<0.0001
Acarbose use	333 (14.3)	290 (16.2)	0.08
Incretin mimetic use	355 (15.2)	270 (15.1)	0.9

Values are expressed as *n* (%) or mean ± SD

^a Includes those with at least one visit after transition

^b Includes those taking 0 U

was ≥6.5%, the 2,333 who achieved an HbA_{1c} before transition of <6.5% were more likely to be male, older and have shorter-duration diabetes, and have access to a certified diabetes educator (CDE) at their investigative site at baseline. Prior to initiating intensive therapy at the time of randomisation, this group also had lower HbA_{1c} levels and less use of insulin, but greater use of sulfonylureas and a higher BMI. At the pre-transition visit, they continued to require less insulin, but were more likely to be taking other glucose-lowering medications, including metformin, thiazolidinediones and secretagogues, than those who did not achieve an HbA_{1c} <6.5% during intensive management.

These 4,119 participants were followed for a mean ± SD of 1.1±0.2 years (range 0.4–1.4) after their glycaemic management approach was relaxed to the standard glycaemic approach. At the time of the final visit, 711 participants continued to have an HbA_{1c} <6.5%, 1,622 had a rise from <6.5% to ≥6.5%, 112 participants had a fall from ≥6.5% to <6.5%, and 1,674 maintained an HbA_{1c} ≥6.5%. Among the 823

participants with a final HbA_{1c} <6.5%, mean HbA_{1c} was 6.0±0.3% (42±3 mmol/mol), and among those with a final HbA_{1c} ≥6.5%, the mean was 7.7±1.1% (61±12 mmol/mol). More participants whose final HbA_{1c} was <6.5% had lost weight and reduced their dose of insulin and use of secretagogues and acarbose from the pre-transition visit to the final post-transition visit compared with those who did not achieve a final HbA_{1c} of <6.5% (Table 2).

Achieving a pre-transition HbA_{1c} <6.5% was a strong predictor of maintaining a final HbA_{1c} <6.5% (crude RR 4.9 [95% CI 4.0, 5.9], *p*<0.0001) (Fig. 1). This strong association was maintained even after adjustment for age, sex, diabetes duration, availability of a CDE at the study site, allocation to intensive blood pressure control, allocation to receive fibrates, pre-randomisation HbA_{1c}, BMI and glucose-lowering medication use, and pre-transition BMI and glucose-lowering medication use (RR 4.0 [95% CI 3.3, 5.0], *p*<0.0001). Adjustment for change in both BMI and glucose-lowering medication use

Table 2 Changes in BMI and medication use from the last pre-transition visit to study completion

Characteristic	Change from pre-transition to final	Final achieved HbA _{1c} <6.5% (n=823)	Final achieved HbA _{1c} ≥6.5% (n=3,296)	p value
BMI	≥3% increase	115 (14.0)	570 (17.3)	<0.0001
	Between -3% and +3%	379 (46.1)	1,697 (51.5)	
	≥3% decrease	329 (40.0)	1,029 (31.2)	
Insulin dose	≥15% increase ^a	51 (6.2)	624 (18.9)	<0.0001
	Between -15% and +15% ^b	464 (56.4)	1,681 (51.0)	
	≥15% decrease ^c	308 (37.4)	991 (30.1)	
Metformin	Added/continued	585 (71.1)	2,423 (73.5)	0.2
	Never prescribed/discontinued	238 (28.9)	873 (26.5)	
Thiazolidinedione	Added/continued	211 (25.6)	888 (26.9)	0.4
	Never prescribed/discontinued	612 (74.4)	24.8 (73.1)	
Secretagogue	Added/continued	334 (40.6)	1,623 (49.2)	<0.0001
	Never prescribed/discontinued	489 (59.4)	1,673 (50.8)	
Acarbose	Added/continued	28 (3.4)	233 (7.1)	0.0001
	Never prescribed/discontinued	795 (96.6)	3,063 (92.9)	
Incretin mimetic	Added/continued	59 (7.2)	271 (8.2)	0.3
	Never prescribed/discontinued	764 (92.8)	3,016 (91.8)	

Values are expressed as n (%)

^a Includes those who started insulin after transition

^b Includes those who were not prescribed insulin at any point before or after transition

^c Includes those who discontinued insulin at or after transition

during the post-transition follow-up also did not alter this association (RR 3.9 [95% CI 3.2, 4.8], $p < 0.0001$). Duration

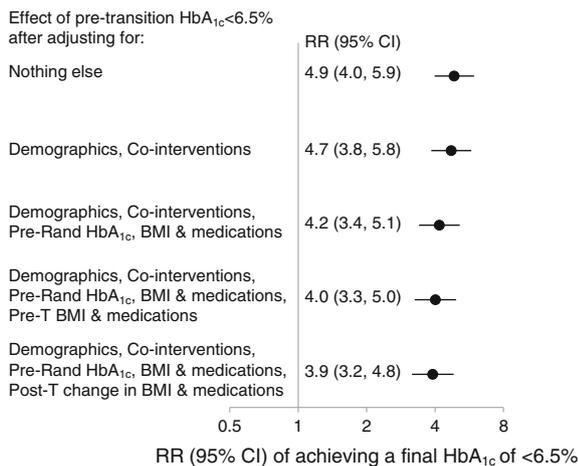


Fig. 1 Effect of having an HbA_{1c} <6.5% (48 mmol/mol) after 4.0 years of intensive diabetes management on the likelihood of having an HbA_{1c} <6.5% 1.1 years after relaxation of glycaemic management. Demographics=sex, age and diabetes duration; Co-interventions=CDE availability at study site, randomisation to fibrate and randomisation to intensive blood pressure control; Pre-Rand=at ACCORD baseline pre-randomisation; Pre-T=last pre-transition; Post-T=post-transition; Pre-T medications=insulin dose (U kg⁻¹ day⁻¹) and use of thiazolidinedione, metformin, secretagogue, acarbose and incretin mimetic before transition; Post-T change in medications=category of change in insulin dose (as in Table 2) and in use of thiazolidinedione, metformin, secretagogue, acarbose and incretin mimetic from before transition to study completion (added, continued, never prescribed, discontinued)

of intensive management was not a significant determinant of final HbA_{1c} (RR 1.05 per year [95% CI 0.99, 1.12], $p = 0.08$).

Figure 2 shows that there was no clear threshold for the effect of progressively lower pre-transition HbA_{1c} on the

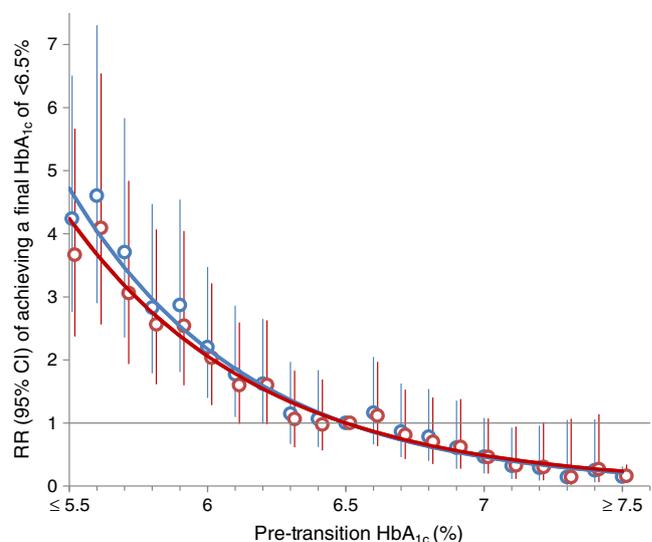


Fig. 2 Prolonged effect of the achieved HbA_{1c} with intensive glycaemic therapy on the likelihood of achieving a final HbA_{1c} <6.5%. Models are unadjusted (blue circles) and adjusted (for demographics, co-interventions, baseline pre-randomisation HbA_{1c}, BMI and medications, and post-transition change in BMI and medications) (red circles). The y-axis displays risks relative to a pre-transition HbA_{1c} of 6.5%. The lines represent a log-linear model assuming a single linear term for pre-transition HbA_{1c}. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

likelihood of achieving an HbA_{1c} <6.5% after relaxation of glycaemic management. Indeed, there was a graded relationship such that those with lower pre-transition HbA_{1c} were more likely to maintain an HbA_{1c} <6.5% over time. Compared with those with a pre-transition HbA_{1c} equal to 6.5%, those with a pre-transition HbA_{1c} of 6.0% or ≤5.5% (37 mmol/mol) were, respectively, 2.2 times [95% CI 1.4, 3.5] or 4.2 times [95% CI 2.8, 6.5] more likely to have an HbA_{1c} <6.5% at the end of follow-up. Adjustment for age, sex, known diabetes duration, availability of a CDE at the study site, allocation to intensive blood pressure control, allocation to receive fibrate, pre-randomisation HbA_{1c}, BMI and glucose-lowering medication use, and change in both BMI and glucose-lowering medication use during the post-transition follow-up minimally affected these estimates (2.0 [95% CI 1.3, 3.2] and 3.7 [95% CI 2.4, 5.7], respectively).

As noted in Fig. 3, there was no relationship between change in HbA_{1c} from pre-transition to the final measurement and the time interval between those two measurements.

Discussion

Achievement of tight glycaemic control for a mean of 4 years was associated with persistent glycaemic control thereafter. This group of people with a median self-reported duration of diabetes of 10 years had an HbA_{1c} >7.5% at baseline, and were intensively managed to a mean of 6.5% at the time of transition. One-fifth of them had an HbA_{1c} <6.5% after a mean of 1.1 years of relaxation from the intensive glycaemic therapy to a standard glycaemic management approach. Those who achieved an HbA_{1c} <6.5% during intensive therapy were four times more likely to have a final post-transition HbA_{1c} below 6.5% compared with those who were not able to achieve such tight control on intensive therapy. This analysis indicates that, in some patients who have established and

initially suboptimally controlled type 2 diabetes, achieving tight glycaemic control with intensive diabetes management is associated with improved maintenance of subsequent glycaemic control despite transition to standard therapy.

There are several potential explanations for the findings, and more than one may have contributed to the observed outcome. First, those who achieved and maintained better glycaemic control may have had physiologically ‘milder’ diabetes with more beta cell reserve or less insulin resistance at entry into the trial. The group with pre-transition HbA_{1c} <6.5% did have shorter known duration of diabetes, and, before initiating intensive management, they had lower HbA_{1c} levels with less insulin use, but more sulfonylurea use and their BMI was higher. Nevertheless, even after adjustment for pre-randomisation and pre-transition characteristics, there was a strong effect of pre-transition HbA_{1c} on post-transition HbA_{1c}. Second, despite the fact that the standard glycaemia approach was used to manage intensive group participants after transition, participants may have continued some unmeasured behaviours and therapies that they were using before transition. It is notable that participants who achieved a final HbA_{1c} <6.5% did so despite greater down-titration of glucose-lowering medications than those who did not achieve a final HbA_{1c} <6.5%. These lifestyle changes and decrease in medication use may have led to more weight loss after transition which reduced insulin resistance, allowing their endogenous insulin to be more effective.

Another possibility is that the period of intensive glycaemic control with multiple agents which resulted in near-normal glycaemia may have ‘rested’ the beta cells and allowed a sustained recovery of beta cell function and/or mass leading to improved glucose homeostasis. Indeed, very early in the course of type 2 diabetes, there is supportive evidence for restoration of glucose homeostasis to the point of remission of diabetes for up to 2 years after 2–6 weeks of intensive management using insulin [6] or oral agents (gliclazide and metformin) [16]. In more longstanding diabetes, short-term continuous subcutaneous insulin infusion [17] and intensive lifestyle intervention [7] have had significant but modest effects. Furthermore, trials in people with impaired fasting glucose and/or impaired glucose tolerance have shown that diabetes can be prevented and/or normal glucose tolerance restored after several years of treatment with therapies that reduce the need to secrete insulin including lifestyle intervention, metformin [18, 19], thiazolidinediones [20, 21], acarbose [22] and insulin [23]. In the present study, this paradigm of therapeutic near-normalisation of glucose is extended to a population with longstanding diabetes using an intensive combination therapy approach. Moreover, this study shows that the nearer to normal that glycated haemoglobin can be brought initially, the more likely sustained maintenance of glucose homeostasis is to be, and this is not simply because it takes longer for HbA_{1c} to drift from lower levels.

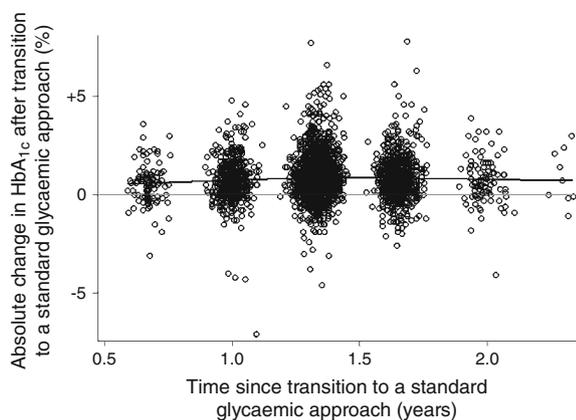


Fig. 3 Effect of time since transition to a standard glycaemic approach on the change in HbA_{1c} since transition. To convert increments for HbA_{1c} in % into mmol/mol, multiply by 10.929

The role of each of the medications used cannot be established in this study. Greater use of metformin, thiazolidinediones and secretagogues was associated with better pre-transition glycaemic control. However, in multivariable regression models, none of the medications or changes in medication was favourably associated with lower post-transition HbA_{1c} (data not shown). Furthermore, adjustment for medications or changes therein did not affect the relationship between pre-transition and post-transition HbA_{1c}, suggesting the types of medications used may be less important than the glycaemic target.

This post hoc analysis was not part of the ACCORD protocol, and must be interpreted with caution. However, the observation is consistent with the existing literature [2–7]. Additional limitations include the absence of a comparison group that did not relax glycaemic management. Nonetheless, both the intensive phase and the relaxation to a standard approach were conducted according to a structured protocol, and information about important covariates was systematically collected for all the 4,119 participants over the full intensive intervention period and the relatively long post-transition follow-up to allow adjustment for potential confounders. Finally, the postulated protection of beta cell function cannot be directly confirmed because of lack of physiological measurements in the ACCORD population.

Questions remain about the optimal duration and type of therapy, and the best candidate patients for this approach, especially in light of the ACCORD Trial finding of increased mortality in the intensive management group [10]. Of note, however, the subgroup of intensively treated participants that benefited here (those who achieve an HbA_{1c} <6.5%) did not have an increased risk of mortality in the ACCORD Trial [24]. The potential benefits and harms of maintaining an HbA_{1c} <6.5% despite relaxing therapy to target a higher HbA_{1c} are unknown.

In summary, the results show that attainment of HbA_{1c} levels below the diabetes threshold level of 6.5% during a mean 4 year period of intensive glycaemic control using a combination of agents is associated with subsequent durable glycaemic control. The relative contributions from physiological vs behavioural changes remain unknown, but the main observation is consistent with other lines of evidence suggesting that the progressive deterioration in glucose homeostasis is not necessarily irreversible in people with established type 2 diabetes.

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Contribution statement HCG, DLS and MEM designed the study. MEM analysed the data. All coauthors contributed to data collection and/or interpretation. ZP and HCG drafted the manuscript and all other coauthors provided critical revisions. All coauthors approved the final version. ZP is responsible for the integrity of the work as a whole.

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