Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial

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Summary

Background **Hyperglycaemia could substantially increase the risk of ischaemic heart disease in patients with type 2 diabetes. We investigated whether intensive lowering of glucose concentrations affects risk.**

Methods **We assessed 10 251 adults aged 40–79 years with established type 2 diabetes, mean glycated haemoglobin A_{1c} (HbA_{1c}) concentration of 67 mmol/mol (8·3%), and risk factors for ischaemic heart disease enrolled in the ACCORD trial. Participants were assigned to intensive or standard therapy (target HbA_{1c} less than 42 or 53–63 mmol/mol [less than 6·0% or 7·0–7·9%], respectively). We assessed fatal or non-fatal myocardial infarction, coronary revascularisation, unstable angina, and new angina during active treatment (mean 3·7 years) plus a further mean 1·2 years. This trial is registered with ClinicalTrials.gov, number NCT00000620.**

Findings **Myocardial infarction was less frequent in the intensive than in the standard therapy group during active treatment (hazard ratio [HR] 0·80, 95% CI 0·67–0·96; p=0·015) and overall (0·84, 0·72–0·97; p=0·02). Findings were similar for combined myocardial infarction, coronary revascularisation, and unstable angina (active treatment HR 0·89, 95% CI 0·79–0·99, overall 0·87 0·79–0·96) and for coronary revascularisation alone (0·84, 0·75–0·94) and unstable angina alone (0·81, 0·67–0·97) during full follow-up. With lowest achieved HbA_{1C} concentrations included as a time-dependent covariate, all hazards became non-significant.**

Interpretation **Raised glucose concentration is a modifiable risk factor for ischaemic heart disease in middle-aged people with type 2 diabetes and other cardiovascular risk factors.**

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Introduction

People with type 2 diabetes have a two to three times higher incidence of ischaemic heart disease than people without diabetes, even when other risk factors are taken into account.[1,2] Reasons for this difference are unclear. Diabetes, however, is defined on the basis of raised glucose concentrations.[3] As the incidence of ischaemic heart disease increases with increasing glycated haemoglobin A_{1c} (HbA_{1c}) concentrations,[4] glucose concentrations might be an important contributing factor. This possibility is supported by the finding that 10 years of intensive compared with standard glucose-lowering therapy reduces the 20-year risk of myocardial infarction by 15% in people with newly diagnosed type 2 diabetes.[5] Additionally, a meta-analysis of four large trials showed 15% reduced incidence of total myocardial infarction (95% CI 6–24) during a mean follow-up period of 4·4 years.[6]

The ACCORD trial was a large North American trial of intense versus standard glucose-lowering therapy in people with established type 2 diabetes and additional risk factors for cardiovascular disease. As previously reported the intervention had a non-significant effect on the primary composite cardiovascular outcome. The incidence of non-fatal myocardial infarction, however, was decreased, whereas the risk of death, particularly from cardiovascular causes, was increased. The effect on cardiovascular mortality remains unexplained. Exploratory analyses have so far identified no relation with severe hypoglycaemia,[7] the degree or speed of glucose lowering,[8] or other potential factors.[9–11] The reduced rate of ischaemic heart disease in ACCORD was not explored. Here we report the effects of the ACCORD glucose-lowering interventions on indices of ischaemic heart disease, including fatal and non-fatal myocardial infarction and unstable and new-onset angina, and the degree to which change in HbA_{1c} concentration accounts for any of these effects.

Methods

Design

The design and results of the ACCORD trial have been published previously.[12,13] Briefly, 10 251 men and women aged 40–79 years with established type 2 diabetes (mean duration 10 years), a mean $gHbA_{1c}$ concentration of 67 mmol/mol (8·3%), and either previous cardiovascular events or risk factors for cardiovascular disease were recruited from 77 clinical centres in the USA and

Canada. Participants were randomly allocated to either intensive glucose-lowering therapy, with a target HbA_{1c} concentration of less than 42 mmol/mol (6·0%), or to standard glucose-lowering therapy, with a target concentration of 53–63 mmol/mol (7·0–7·9%). The medications used to achieve these targets were the same in the two groups and included metformin, short-acting and long-acting insulins, sulfonylureas, meglitinides, thiazolidinediones, acarbose, and incretins. Participants were concomitantly enrolled in either a blood pressure trial (intense *vs* standard reduction)[14] or a lipid trial (optimised statin therapy with or without fenofibrate *vs* placebo),[15] in a double two-by-two factorial design. Patients were followed up at least every 4 months to ensure therapeutic goals were met and maintained and to monitor outcomes and adverse effects. The study protocol was approved by the ethics committee of each study centre, and approved and monitored by an independent data safety and monitoring board. All participants provided written informed consent.

	Intensive treatment (n=5128)	Standard treatment (n=5123)
Baseline		
Age at baseline (years)	62 (7)	62 (7)
Women	1983 (38·7%)	1969 (38·4%)
Previous myocardial infarction	909 (17·7%)	925 (18·1%)
Previous angina	608 (11·9%)	560 (10·9%)
Previous revascularisation	1185 (23·1%)	1112 (21·7%)
Follow-up		
Treatment transition		
Median (IQR) duration (years)*	3·7 (2·8–4·5)	3·7 (2·9–4·5)
Duration (years)*	3·7 (1·4)	3·7 (1·4)
Total follow-up (person-years)	19 497	19 535
Last HbA_{1c} concentration (mmol/mol, %)	49 (7·4), 6·6 (1·0)	61 (8·7), 7·7 (1·1)
Median (IQR) last HbA_{1c} concentration (mmol/mol, %)	46 (42–53), 6·4 (6·0–7·0)	59 (53–66), 7·5 (7·0–8·2)
Last ACE inhibitor or ARB use recorded	1830 (37·0%)	1874 (37·6%)
Last statin use recorded	3829 (74·7%)	3833 (74·9%)
Last aspirin use recorded	3020 (58·9%)	3002 (58·6%)
Last SBP (mm Hg)	128 (17)	129 (17)
Last DBP (mm Hg)	67 (11)	68 (11)
Last serum LDL cholesterol concentration (mmol/L)	2·3 (0·9)	2·3 (0·9)
Last serum creatinine concentration (mmol/L)	97 (35)	97 (35)
Study end		
Median (IQR) follow-up (years)†	4·8 (4·0–5·7)	4·8 (4·0–5·7)
Follow-up (years)†	4·8 (1·6)	4·7 (1·6)
Total follow-up (person-years)	25 048	25 162
Last HbA_{1c} concentration (mmol/mol, %)	56 (9·2), 7·3 (1·2)	62 (8·7), 7·8 (1·2)
Median (IQR) last HbA_{1c} concentration (mmol/mol, %)	54 (48–63), 7·1 (6·5–7·9)	60 (53–68), 7·6 (7·0–8·4)
Last ACE inhibitor or ARB use recorded	1855 (37·2%)	1915 (38·3%)
Last statin use recorded	3819 (74·5)	3843 (75·0)
Last aspirin use recorded	3133 (61·1)	3156 (61·6)
Last SBP (mm Hg)	129 (18)	129 (17)
Last DBP (mm Hg)	68 (11)	68 (10)
Last serum LDL cholesterol concentration (mmol/L)	2·3 (0·9)	2·3 (0·9)
Last serum creatinine concentration (mmol/L)	97 (35)	97 (44)

Data are mean (SD) or number (%) unless otherwise stated. HbA_{1c}=glycated haemoglobin A_{1c}. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. SBP=systolic blood pressure. DBP=diastolic blood pressure. *Time from randomisation to occurrence of primary outcome, censoring date, or last day before treatment transition. †Time from randomisation until initial occurrence of primary outcome, censoring date, or exit visit.

***Table*: Ischaemic heart disease risk factors and event rates**

Outcomes

The prespecified primary outcome of ACCORD was the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death, defined as death that was unexpected or presumed to be due to cardiovascular disease, congestive heart failure, myocardial infarction, stroke, other cardiovascular disease, a study procedure, or arrhythmia.[12,13] Secondary outcomes were as follows: death from any cause; the primary outcome plus first occurrence of revascularisation or hospitalisation for heart failure; combined first occurrences of cardiovascular death, non-fatal myocardial infarction, and unstable angina; any stroke; and any congestive heart failure.[15] Coronary revascularisation was defined as percutaneous coronary intervention, with or without a stent, or coronary artery bypass surgery. Unstable angina was defined as self-reported new, accelerated, or rest angina plus ischaemia on ECG, evidence of stenosis on angiography, or both, and new-onset angina was defined as the first time an event was recorded on the case report form as new-onset exertional angina. Outcomes were adjudicated centrally by researchers unaware of treatment allocations.

Treatment transition

Intensive therapy was discontinued after the data safety and monitoring board detected increases in all-cause and cardiovascular mortality. Participants were switched to the standard regimen on Feb 5, 2008, after a mean follow-up period of 3·7 years (treatment transition). All participants continued to be followed up in the blood pressure and lipid trials for a mean period of 1·2 years.

Statistical analysis

All statistical analyses were done at the ACCORD coordinating centre with SAS (version 9.3). Continuous data were summarised as mean (SD), median (IQR), or number (%). Event rates were estimated as the number of events divided by the total person-years of follow-up, and expressed as the number per 100 person-years. Analyses were done according to intention to treat, with separate assessment for outcomes accrued between randomisation and treatment transition and those accrued from randomisation until the end of follow-up. Mean or median values for HbA_{1c}, LDL cholesterol, and creatinine concentrations in serum, blood pressure,

and the use of cardioprotective drugs were calculated from the latest data collected before treatment transition and the end of follow-up. We used cumulative incidence plots for death as a competing risk[16] to estimate the cumulative proportions of participants who had each type of event during the two follow-up periods.

We adopted the approach of Fine and Gray[17] to fit proportional subdistribution hazard models to survival data with competing risks and to estimate the hazard ratios (95% CI) for the two follow-up periods. These models included a term representing treatment assignment plus terms accounting for participation in the blood pressure or lipid trial, assignment to the intensive blood pressure intervention in the blood pressure trial, assignment to fenofibrate in the lipid trial, and the presence or absence of previous cardiovascular disease. We did an exploratory analysis to investigate whether any effects the glucose-lowering intervention had on analysed outcomes could be attributable to the change in HbA_{1c} achieved before treatment transition. Hazard ratios were recalculated taking into account HbA_{1c} concentration as a time-dependent covariate (ie, new results were obtained every 4 months). We took p values less than 0·05 to be significant.

Role of the funding source

The funder of the study participated in the study design, data analysis, and data interpretation. The funder had no role in data collection or writing of this report. 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

No significant differences were seen between groups for baseline characteristics, or for blood pressure, LDL cholesterol and creatinine concentrations, or use of cardiovascular drugs during follow-up (table). Patients were followed up for a mean of 3·7 years until the date of transition, and a mean of 4·8 years until the end of full follow-up. Greater numbers of all classes of glucose-lowering drugs and combinations had been used in the intensive treatment group than in the standard group at the end of the active treatment period.[12]

1263 ischaemic heart disease events were reported during the active period and 1619 during the entire follow-up period. Fewer participants in the intensive therapy group experienced a myocardial infarction, a non-fatal myocardial infarction, or the composite

	Number of events (annual incidence [%])		Hazard ratio (95% CI) intensive *vs* standard	p value
	Intensive	Standard		
Fatal or non-fatal MI				
Treatment transition	220 (1·15%)	267 (1·41%)	0·80 (0·67–0·96)	0·015
Full follow-up	304 (1·25%)	355 (1·46%)	0·84 (0·72–0·97)	0·021
Fatal MI				
Treatment transition	20 (0·10%)	12 (0·06%)	1·63 (0·80–3·32)	0·178
Full follow-up	24 (0·09%)	14 (0·05%)	1·68 (0·87–3·24)	0·121
Non-fatal MI				
Treatment transition	207 (1·08%)	257 (1·35%)	0·78 (0·65–0·94)	0·009
Full follow-up	287 (1·18%)	344 (1·42%)	0·81 (0·70–0·95)	0·010
Coronary revascularisation				
Treatment transition	469 (2·54%)	517 (2·81%)	0·89 (0·78–1·01)	0·063
Full follow-up	565 (2·41%)	658 (2·81%)	0·84 (0·75–0·94)	0·003
Unstable angina				
Treatment transition	168 (0·88%)	199 (1·04%)	0·83 (0·68–1·02)	0·074
Full follow-up	202 (0·83%)	245 (1·00%)	0·81 (0·67–0·97)	0·023
Any MI/unstable angina/coronary revascularisation				
Treatment transition	601 (3·31%)	662 (3·66%)	0·89 (0·79–0·99)	0·031
Full follow-up	764 (3·32%)	855 (3·74%)	0·87 (0·79–0·96)	0·006
Any MI/unstable angina				
Treatment transition	333 (1·77%)	408 (2·19%)	0·79 (0·69–0·92)	0·002
Full follow-up	454 (1·90%)	535 (2·25%)	0·83 (0·73–0·94)	0·003
New-onset angina				
Treatment transition	48 (0·25%)	66 (0·34%)	0·73 (0·50–1·05)	0·092
Full follow-up	63 (0·25%)	82 (0·33%)	0·76 (0·55–1·06)	0·110

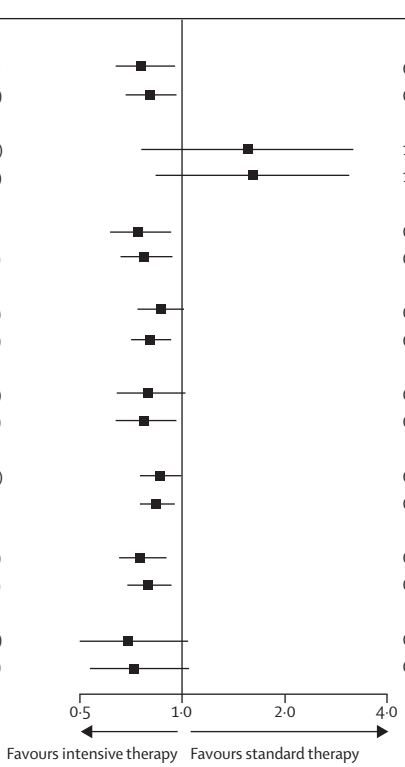

Figure 1: **Incidence and risk of ischaemic heart disease events, by follow-up period**
The numbers for the composite outcome of any MI or unstable angina shown in the figure differ from those in a previous report[12] owing to a typographical error; the numbers in the previous report should have referred to non-stroke cardiovascular death, non-fatal MI, or unstable angina. MI=myocardial infarction.

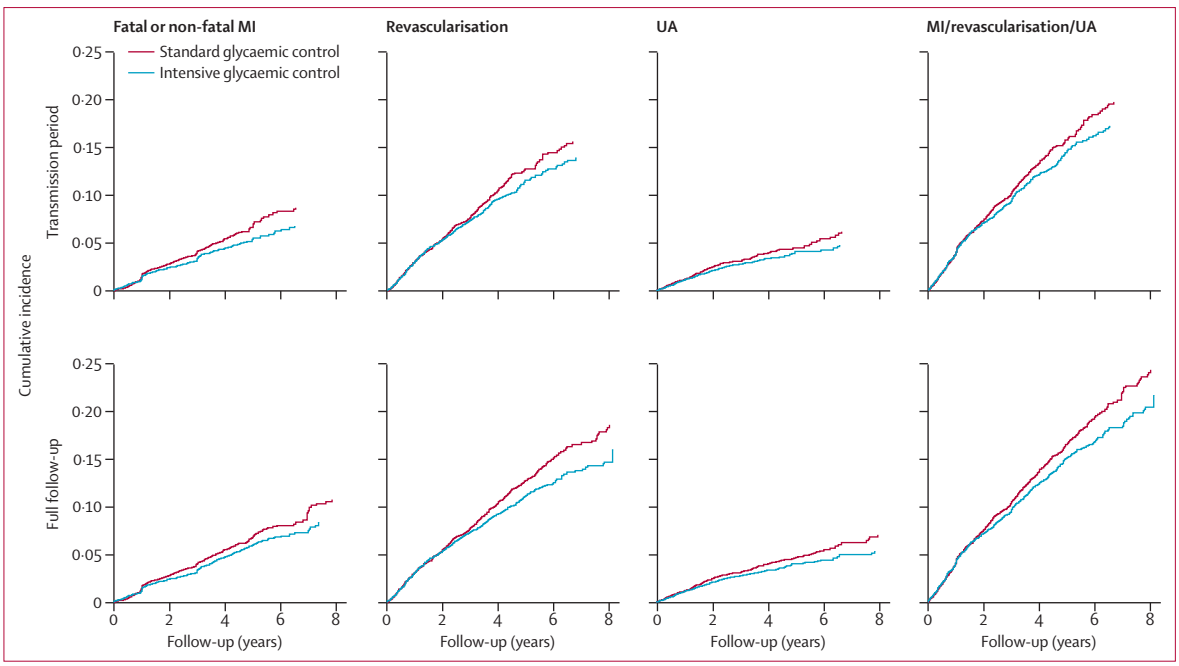

Figure 2: **Cumulative incidence of ischaemic heart disease outcomes up to treatment transition and up to the end of the study**
The data up to treatment transition take into account competing risk due to death. MI=myocardial infarction. UA=unstable angina.

See Online for appendix

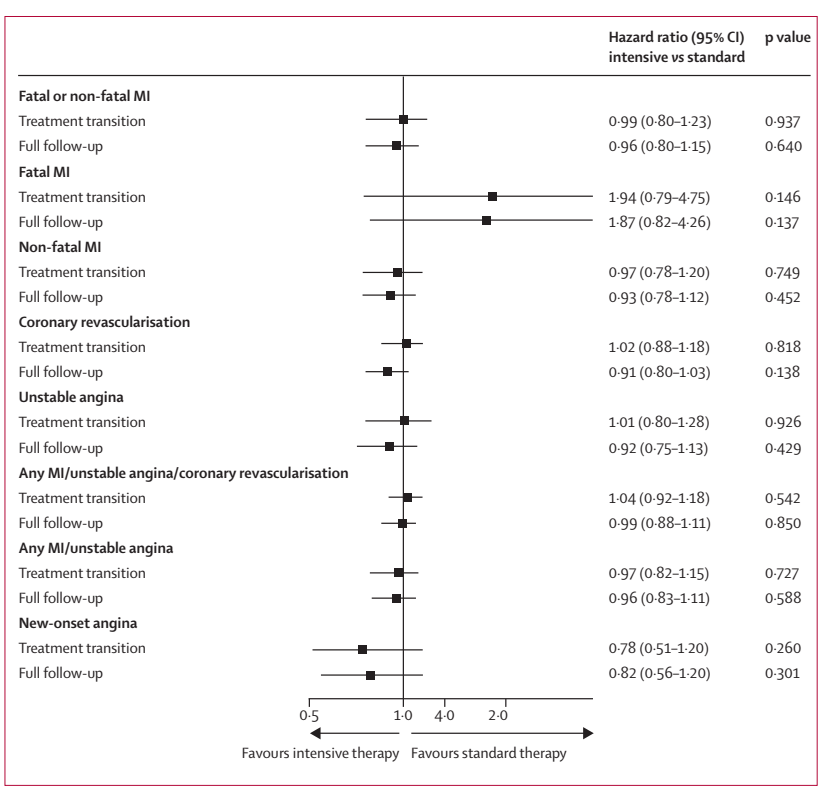

Figure 3: **Risk of ischaemic heart disease events after adjustment for glycated haemoglobin A_{1c} concentrations achieved during active treatment, by follow-up period**
Glycated haemoglobin A_{1c} concentrations were included as a time-dependent covariate and take account of competing risk due to death. MI=myocardial infarction.

outcome of any myocardial infarction or unstable angina than in the standard therapy group in both follow-up periods (figure 1). Compared with the standard therapy group, participants in the intensive therapy group were 20% less likely to have any myocardial infarction during the active treatment period and 16% less likely during the entire follow-up period (figure 1). Findings were similar for the composite ischaemic heart disease outcome of myocardial infarction, unstable angina, or coronary revascularisation (figure 1). Lower rates of coronary revascularisation alone or unstable angina alone were seen in the intensive group for the entire treatment period but not before treatment transition (figure 1). The intervention had no significant effect on fatal myocardial infarction or new angina. Cumulative incidence curves for all outcomes were lower with intensive therapy in both follow-up periods (figure 2, appendix).

The addition of the HbA_{1c} concentration measured during the active treatment period as a time-dependent covariate to the hazard analysis attenuated all the significant hazard ratios to neutral and did not change the significance of the non-significant hazard ratios (figure 3).

Discussion

Intensive therapy was associated with significant reductions in the 5-year incidence of ischaemic heart disease (13%), any myocardial infarction (16%), non-fatal myocardial infarction (19%), coronary revascularisation (16%), and unstable angina (19%). These analyses were not prespecified in the ACCORD protocol, but our

findings are consistent with those from other large outcomes trials where intensive glucose-lowering therapy reduced the incidence of fatal and non-fatal myocardial infarction in patients with type 2 diabetes (panel).[6] That these effects were evident before treatment transition and increased during further follow-up are consistent with at least one other trial done in people with type 2 diabetes.[5] Moreover, the finding that adjustment for HbA_{1c} concentrations achieved before treatment transition rendered these effects non-significant supports the hypothesis that the degree of glucose lowering or some closely related factor accounts for the effect of the intervention on ischaemic heart disease. Finally the effect was consistent across different measures of ischaemic heart disease. Together with the evidence that individuals with genetic markers of hyperglycaemia have higher glucose concentrations and are more likely to develop cardiovascular disease than those without these markers,[18] these findings suggest that rising glucose concentration is a modifiable risk factor for ischaemic heart disease.

The beneficial effect of the intensive glucose-lowering intervention on ischaemic heart disease is at odds with the ACCORD finding of increased risk of death from cardiovascular causes compared with the standard intervention. It is also at odds with the observation that the intensive intervention did not reduce fatal myocardial infarction. A possible explanation for these discrepancies is suggested by the findings of an epidemiological analysis of ACCORD, where much of the mortality in the intensive treatment group occurred in people whose HbA_{1c} concentrations did not decrease from baseline.[7] Therefore, individuals whose glucose levels do not fall in response to intensive intervention, presumably due to unknown behavioural or biological factors, might have been harmed by persistent but futile attempts to lower glucose concentrations. Alternatively, the mortality in ACCORD could have been a chance finding.[11] This possibility is supported by the inability so far to identify any specific reason for this outcome.[7,8,10] Additionally, some of the fatal myocardial infarctions might have been misclassified as other cardiovascular deaths. Irrespective of the explanation, the fact that more than 80% of the cardiovascular deaths were judged not to be attributable to a myocardial infarction,[12,13] and the reduced risk of ischaemic heart disease events with the intensive glucose-lowering intervention, suggest that ischaemic heart disease might not be related to mortality in the ACCORD intensive therapy group.

Owing to this analysis not being planned, our findings could be due to chance and, therefore, not reproducible. The large number of statistical tests and the overlap between the various indices of ischaemic heart disease potentially increase the risk of chance. Moreover, the low number of fatal myocardial infarctions does not provide enough power to clearly estimate the effect of the intervention on fatal ischaemic heart disease or to rule out the possibility of divergent effects on fatal compared with non-fatal ischaemic heart disease. Strengths of this analysis include the randomised design, the large number of non-fatal events, and the high ascertainment of outcomes.

Whereas our findings suggest that glucose-lowering interventions can reduce the risk of ischaemic heart disease, they do not nullify the previous observation that the overall cardiovascular benefits of 3·7 years of intensive glycaemic control are outweighed by the risk of death. Nevertheless, they are consistent with the hypothesis that dyglycaemia is causally related to ischaemic heart disease and strongly indicate the need for further investigation of this relation.

Panel: Research in context

Systematic review

The effect of intensive glucose lowering on cardiovascular outcomes in people with type 2 diabetes remains unclear. Four large outcomes trials allocated people with type 2 diabetes to intensive versus standard glucose-lowering regimens and assessed the effects of the intervention on various cardiovascular outcomes. A meta-analysis of data from these trials reported that the incidence of fatal and non-fatal myocardial infarction was reduced by 15% (95% CI 6–24) during a mean follow-up period of 4·4 years.[6] By contrast, the treatment approach had no effect on fatal or non-fatal stroke. The ACCORD trial involved intense versus standard glucose-lowering therapy in people with established type 2 diabetes and additional cardiovascular risk factors. Although no significant effect was found on the primary composite cardiovascular outcome, the incidence of non-fatal myocardial infarction decreased, whereas death, especially cardiovascular deaths, increased. We therefore decided to use the ACCORD data to assess the relation between glucose lowering and ischaemic heart disease.

Interpretation

Intensive glucose-lowering therapy was associated with reduced risks of any myocardial infarction, coronary revascularisation, and unstable angina, when assessed separately and in combination, during a mean treatment period of 3·7 years. Further reductions were seen during an additional follow-up period of 1·2 years after the intensive treatment had been stopped. Although this analysis was not prespecified, our findings suggest that further investigation of this relation could identify individuals in whom the benefit of glycaemic control would clearly outweigh any harm.

Contributors

All authors participated in acquiring and interpreting the data. HCG and MEM wrote the first draft of the report, MEM completed the statistical analyses, and FI-B, JL, CM, HAL, and GLB revised the drafts and approved the final version.

Declaration of interests

HCG has received grants from the National Heart, Lung, and Blood Institute, Sanofi, and Lilly, and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffman LaRoche, Novo Nordisk, and Sanofi. FI-B has received grants from the National Institutes of Health and Novo Nordisk. JL has received grants from the National Institutes of Health, Andromeda, Boehringer Ingelheim, GI Dynamics, Halozyme, Hoffman LaRoche, Immune Tolerance Network, Jaeb Center for Health Research, Johnson & Johnson, Lexicon, Lilly, Merck, Novo Nordisk, Orexigen, phase Bio, Sanofi, and Tolerx, and personal fees from Dexcon, Sanofi, Takeda, Valeritas, and Vivus. CM has received grants from Bristol-Myers Squibb, Eli Lilly, Hoffman LaRoche, GlaxoSmithKline, Merck Frosst, Novo Nordisk, and Sanofi, and personal fees and non-financial support from Novo Nordisk. HAL has received grants from Amylin, Boehringer Ingelheim, Lilly, and Sanofi. The other authors declare that they have no competing interests.

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