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RESEARCH ARTICLE

Intensive glucose control and recurrent cardiovascular events: 14-year follow-up investigation of the ACCORDION study

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Abstract

Aims: While cardiovascular disease in patients with type 2 diabetes commonly progresses with the occurrence of repeated events, most trials consider the effect of glucose-lowering strategies only on the first event. We examined the Action to Control Cardiovascular Risk in Diabetes trial and its observational follow-up study (ACCORDION) to investigate the effect of intensive glucose control on multiple events and further identify any subgroup effects.

Materials and Methods: A recurrent events analysis, using a negative binomial regression model, was applied to estimate the treatment effect on different consecutive cardiovascular disease events, including non-fatal myocardial infarction, non-fatal stroke, hospitalisation from heart failure, and cardiovascular death. Interaction terms were used to identify potential effect modifiers. The robustness of the results was confirmed in sensitivity analyses using alternative models.

Results: The median duration of follow-up was 7.7 years. Of the 5128 participants in the intensive and 5123 in the standard glucose control arm, respectively, 822 (16.0%) and 840 (16.4%) participants experienced a single event; 189 (3.7%) and 214 (4.2%) participants experienced two events; 52 (1.0%) and 40 (0.8%) experienced three events; and 1 (0.02%) and 1 (0.02%) experienced four events. There was no evidence of a treatment effect, with a rate difference of 0.0 (−0.3, 0.3) per 100 person-years comparing intensive versus standard intervention, although with non-significantly lower event rates in younger patients with HbA1c $< 7\%$ and higher event rates in older patients with HbA1c $\geq 9\%$.

Discussion: Intensive glucose control may not affect cardiovascular disease progression except in select subgroups. Since time-to-first event analysis may miss beneficial or harmful effects of glucose control on the risk of cardiovascular disease, recurrent events analysis should be routinely analysed in cardiovascular outcome trials, particularly when investigating long-term treatment effects.

Clinical trial reg no. NCT00000620, clinicaltrials.gov.

KEYWORDS
cardiovascular diseases, diabetes mellitus, randomized controlled trial, type 2 diabetes

1 | INTRODUCTION

The role of intensive glucose control to reduce the risk of cardiovascular disease has long been a source of uncertainty in the management of people with type 2 diabetes. While evidence for a reduction in the risk of microvascular events is established, the effects of specific glycated haemoglobin (HbA1c) targets on the risk of macrovascular events and death are more varied across studies and different patient populations.[1,2] The landmark Action to Control Cardiovascular Risk in Diabetes (ACCORD) (NCT00000620) trial concluded that in individuals at high cardiovascular risk, a mean of 3.7 years of intensive glucose control may increase mortality, while not affecting the composite primary outcome of Major Adverse Cardiovascular Events (MACE).[3] Post hoc-studies of the ACCORD have also highlighted some factors, including neuropathy or retinopathy, that may be associated with a differential effect of intensive glucose control.[4–9] By contrast, the observational ACCORD Follow-on (ACCORDION) found neutral effects of intensive glucose control on mortality but an increase in cardiovascular death after 9 years.[10]

As in ACCORD, most subsequent Cardiovascular Outcome Trials (CVOTs) investigating the effects of single therapeutic agents or glucose-lowering strategies on different types of macrovascular events utilised a single composite endpoint of MACE as their primary outcome. This practice reflects the shared pathophysiology and clinical importance of coronary, cerebrovascular, and other macrovascular diseases and allows any treatment effects to emerge more clearly by increasing the number of events despite decreasing mortality rates.[11] Usually, only the first event of any type is considered, despite the fact that cardiovascular disease is progressive, such that one event may increase the risk of subsequent events.[12–15] As multifactorial risk factor control and better acute management of vascular events may be helping to increase the life expectancy of people with type 2 diabetes, this also leaves more time for macrovascular complications to develop and recur in these patients.[16]

Another approach then is to consider multiple events. Indeed, some CVOTs have looked at the total number of events and demonstrated the safety and efficacy of individual drugs beyond a first event.[17–20] In cases where drugs have pleiotropic effects or where exacerbations are a feature of the disease, such as in heart failure, a recurrent or total events analysis may be a natural approach.[21,22] Moreover, for patients with diabetes, the total disease burden is central to the possibility of a legacy effect in which the benefits of glucose control emerge only after a long follow-up as complications are allowed to accumulate.[23–25]

Despite the importance of shifting the perspective from the first event towards the total burden of events to understand the role of intensive glucose control, evidence from large trials is still lacking. Therefore, we used data from the ACCORD and ACCORDION studies to explore whether intensive treatment was associated with a reduction in the total burden of first occurrences of each of non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, or cardiovascular death. In line with previous post-hoc studies suggesting subgroup-specific effects, we also investigated the presence of effect modification by demographic, clinical and biochemical characteristics.

2 | MATERIALS AND METHODS

2.1 | Study design

We used publicly available individual-level data of participants enroled in the ACCORD trial and its observational follow-up, the ACCORDION study; the details and main results of these two studies have been reported previously.[3,10,26,27] In ACCORD, 10,251 participants with type 2 diabetes and previous evidence, or at high risk, of cardiovascular disease were randomised to intensive (HbA1c target of <6% [42 mmol/mol]) or standard [7%–7.9% (53–63 mmol/mol)] glucose-lowering therapy. At the end of the trial, after a mean of 3.7 years, the intensive treatment was stopped due to excess mortality and participants were treated according to the then-standard glucose-lowering recommendations. Of the 9533 surviving ACCORD participants, 8601 (90.2%) agreed to participate in the ACCORDION observational study and were followed up for a mean of 7.7 years from randomisation.[10]

2.2 | Outcomes

Post-randomisation incident non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, or cardiovascular death events were prospectively collected in the ACCORD study and adjudicated by a masked, independent committee; their definitions have been detailed elsewhere.[26] Importantly, only the first occurrence of each event type was recorded. In the ACCORDION extension, participants were either seen or called to collect information on the same outcomes, confirmed by the support of clinical documentation; in the US, deaths were also confirmed using the National Death Index. For quality control, a random 10% of the outcomes occurring in ACCORDION were also adjudicated.

2.3 | Effect modifiers

Pre-randomisation information was collected on several patients' characteristics, including ophthalmological complications—defined as any history of cataract removal or photocoagulation in either eye; diabetic peripheral neuropathy—defined as any history of

neuropathy; and diabetic nephropathy—measured as a continuous variable using the urine albumin to creatinine ratio (UACR), in line with current guidelines,[28] and as estimated glomerular filtration rate (eGFR), estimated in ACCORD with the Modification of Diet in Renal Disease formula.[28]

2.4 | Statistical analysis

Baseline characteristics are reported by treatment arm and total number of incident events, which included non-fatal myocardial infarction or stroke, hospitalisation for heart failure, or cardiovascular death. The number of person-years was calculated as the total analysis time at risk of all participants combined.

In contrast with the classical approach of investigating rates during follow-up for the first event only (i.e., any of the events defining the composite endpoint outcome), in this analysis participants still contributed to follow-up of other types of non-fatal events; the maximum number of events was therefore four, namely three non-fatal events plus cardiovascular death. Recurrent (repeated) events over time can be investigated using different methods while accounting for the dependence of the events: we considered the negative binomial regression as our main model, with total number of events as outcome and follow-up as offset. This model allows the estimation of the arm-specific rate and of the rate ratio of events comparing intensive versus standard glucose intervention, accounting for the variability in the risk of events within each patient (over-dispersion).[21] For events that occurred on the same day (e.g., non-fatal myocardial infarction and non-fatal stroke), a single nonfatal event was counted.[29] The effect of intensive treatment on the total burden of consecutive cardiovascular disease (CVD) events was also explored in interaction analysis in relation to sex, baseline presence of ophthalmological, neurological, and renal (UACR and eGFR) complications, age, diabetes duration, HbA1c, and body mass index (BMI); for continuous variables, interactions were modelled using a restricted cubic spline transformation (3 knots at the 10th, 50th, and 90th centile of the variable distribution) to assess possible non-linearity.

Differences in the incidence of events were also investigated in sensitivity analyses using two alternative models: we estimated the hazard ratio of intensive versus standard intervention using the Prentice-Williams-Peterson total time (time from randomisation) approach, which accounts for the order of events[30]; and the Andersen-Gill model, a generalisation of the Cox proportional hazards model, which also assumes independence between all event times.[30]

All analyses were conducted in Stata 16.0 and results are reported with 95% confidence interval (CI). The statistical code is available at [*Github*].

3 | RESULTS

3.1 | Baseline characteristics

Of the 10,251 patients enrolled in the ACCORD trial, 5128 were randomised to intensive and 5123 to standard glucose control: as expected in the randomisation process, their characteristics at baseline were balanced, with approximately a third of participants reporting a previous cardiovascular event, a median of 10 years of diabetes duration and 62 years of age, and a median BMI of 32 kg/m^2 and HbA1c of 8.1% [65 mmol/mol]; approximately 60% were men (Supporting Table S1). During the follow-up, 2752 total cardiovascular events occurred: a single event in 1662 subjects, two in 403, three in 92, and four in 2 (Table 1 and Figure 1A). Classical cardiovascular risk factors were more frequent or more severe in subjects

TABLE 1 Baseline characteristics by number of events during follow-up.

No. of total events	0	1	2	3	4
Participants	8092	1662	403	92	2
Age (yr)	62.0 (58.0; 66.0)	63.0 (59.0; 69.0)	65.0 (60.0; 70.0)	67.0 (61.0; 70.5)	63.5 (55.0; 72.0)
Women	3267 (40.4%)	540 (32.5%)	121 (30.0%)	23 (25.0%)	1 (50.0%)
History of CVD	2462 (30.4%)	827 (49.8%)	252 (62.5%)	66 (71.7%)	2 (100%)
Ophthalmic complications	2360 (29.2%)	620 (37.3%)	170 (42.2%)	43 (46.7%)	1 (50.0%)
Neuropathy	2000 (24.7%)	548 (33.0%)	143 (35.5%)	44 (47.8%)	2 (100%)
Diabetes duration (yr)	9.0 (5.0; 15.0)	10.0 (5.5; 16.0)	11.0 (6.0; 18.0)	15.0 (8.0; 21.0)	14.5 (11.0; 18.0)
HbA1c (%)	8.1 (7.5; 8.8)	8.2 (7.7; 9.0)	8.3 (7.7; 9.0)	8.6 (7.8; 9.3)	8.7 (8.6; 8.7)
HbA1c (mmol/mol)	65 (59; 73)	66 (61; 75)	67 (61; 75)	71 (61; 78)	71 (71; 72)
Body-mass index (kg/m^2)	31.7 (28.1; 35.8)	32.0 (28.4; 36.1)	32.2 (28.7; 36.9)	32.8 (29.1; 37.7)	36.9 (36.0; 37.8)
eGFR (mL/min*1.73 m^2)	90 (77; 106)	87 (72; 103)	80 (66; 98)	80 (69; 93)	72 (51; 93)
UACR (mg/g)	13 (7; 37)	22 (9; 92)	36 (11; 156)	61 (14; 243)	69 (11; 127)

Note: Continuous variables are reported as median (interquartile range) and categorical as number (percentage). There were missing data for ophthalmic complications (1 participant); neuropathy (1); diabetes duration (92); HbA1c (22); body-mass index (6); eGFR (54); UACR (433).

Abbreviations: CVD, Cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; UACR, urine albumin to creatinine ratio.

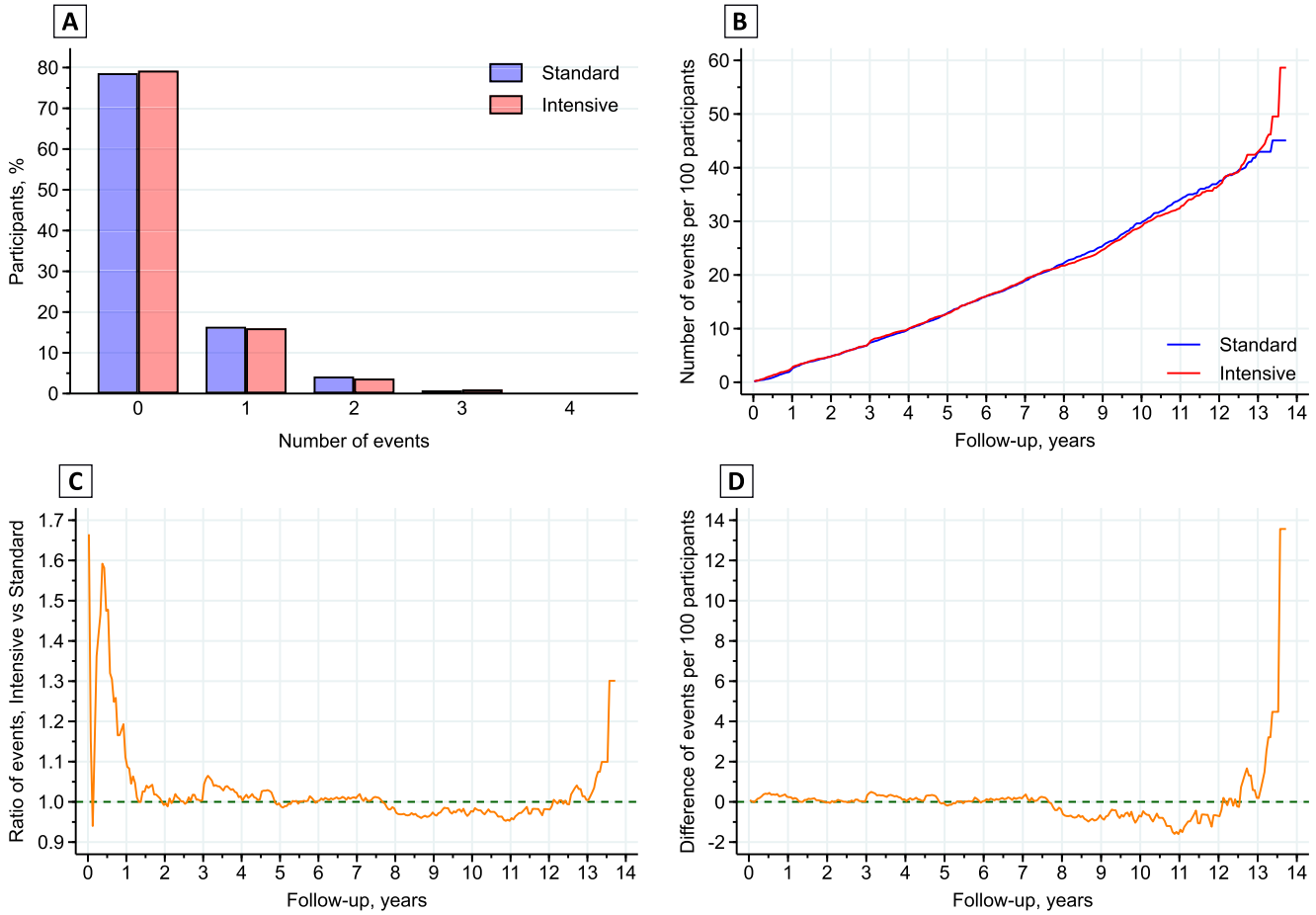

FIGURE 1 Total number of cardiovascular events and death during follow-up. Number of participants across intervention arms and number of events during follow-up (A); mean cumulative number of events over time in standard and intensive treatment arm (B); ratio (C) and difference (D) of mean cumulative number of events over time comparing intensive to standard treatment arm.

who went on to experience a larger number of total cardiovascular events: participants were progressively older (median age: 62 years in subjects with no events vs. 67 in those with three events; Table 1), more frequently men (59.6% vs. 75.0%, respectively), reported a previous cardiovascular event (30.4% vs. 71.7%) and microvascular disease, and had slightly worse kidney function and HbA1c control (median: 8.1% [65 mmol/mol] vs. 8.6% [71 mmol/mol], respectively); a larger number of events was also associated with a longer duration of diabetes at randomisation (median: 9 years in subject with no events vs. 15 in those with three events).

3.2 | Treatment effect

Of the 5128 participants in the intensive and 5123 in the standard glucose control arm, respectively, 822 (16.0%) and 840 (16.4%) experienced a single event (Figure 1A); 189 (3.7%) and 214 (4.2%) two events; 52 (1.0%) and 40 (0.8%) three events; and 1 (0.02%) and 1 (0.02%) four events; 4064 participants (79.3%) and 4028 (78.6%) did not experience any of the investigated events during the study.

During a follow-up of 103,890 person-years, the mean rate of all cardiovascular events per 100 person-years was 3.2 (95% CI: 3.0, 3.4) in participants randomised to standard glucose control and 3.1 (95% CI: 2.9, 3.3) in those randomised to intensive glucose control, corresponding to a rate ratio of 1.00 (0.91, 1.10) and a rate difference of 0.0 (−0.3, 0.3) per 100 person-years comparing intensive versus standard intervention. In comparison, using the common approach of a composite outcome analysis limited to the occurrence of the first event only, the rates were 2.7 (2.5, 2.8) and 2.8 (2.6, 3.0) per 100 person-years in the intensive and standard glucose control intervention, respectively, corresponding to a rate ratio of 0.96 (0.88, 1.04) and a rate difference of −0.1 (−0.3, 0.1) per 100 person-years comparing intensive versus standard intervention (Supporting Figure S1).

The number of total cardiovascular events during follow-up progressively increased in both arms, with approximately 631 and 643 events at 5 years in subjects randomised to intensive versus standard glucose control, increasing respectively to 1255 and 1295 at 10 years, and 1349 and 1389 at 13 years (Figure 1B). The negligible differences in the total number of events over time comparing the two interventions are shown in Figure 1C,D: the ratio of events

(intensive vs. standard) changed significantly only during the first year of observation (Figure 1C) although such variation corresponded to virtually no absolute risk difference (Figure 1D) given the very low number of cumulative events at the beginning of the trial. The greatest discrepancies between intensive and standard treatment arms were observed at the extremes of the study period, with the largest ratio of events at 0 years (1.7 events per 100 person-years; Figure 1C) and the largest absolute difference at 13.7 years (13.6 events per 100 person-years; Figure 1D).

Rates in total cardiovascular events comparing the two arms were very similar across sex and baseline diabetes complications (Figure 2): comparing intensive versus standard, the minimum difference was 0.1 per 100 person-years in men and the maximum 0.8 per 100 person-years in subjects reporting neuropathy. However, regardless of the intervention effect, rates varied considerably across the characteristics. The presence of CVD at baseline was associated with the largest difference, from around 2 per 100 person-years in subjects without CVD to 5 in those with CVD. The effect of the intervention on total cardiovascular events was negligible in relation to diabetes duration, BMI, eGFR, and UACR (Figure 3). Conversely, a greater rate ratio (i.e., lower efficacy of the intervention) was observed for a progressive linear increase in age, while a lower rate ratio (i.e., greater efficacy) was observed for baseline HbA1c values between 8% [64 mmol/mol] and 8.9% [74 mmol/mol].

The combined effect of age and HbA1c is shown in Figures S2 and S3. Generally, event rates in both arms increased with age across different levels of baseline HbA1c. Notably, in subjects with HbA1c <7% [53 mmol/mol] on standard treatment, event rates did not increase with age; and in subjects with HbA1c ≥ 9% [74 mmol/mol], event rates increased much more quickly with older age on intensive treatment compared to standard treatment (Figure S2). There were no statistically significant differences in the event rates by treatment arm across age and HbA1c (Figure S3). However, a trend emerged: older age was associated with a lower benefit of intensive glucose reduction. This was most pronounced for baseline values of HbA1c <7% and ≥9%: for HbA1c < 7% (53 mmol/mol) the mean rate differences comparing intensive versus standard treatment increased from −1.7 (95% CI: −3.6, 0.3) per 100 person-years in a 50-year old participant to 1.6 (−1.5, 4.7) in a 76-year old participant; corresponding estimates for HbA1c ≥ 9% (75 mmol/mol) were −0.4 (−1.3, 0.5) and 2.3 (−0.5, 5.1).

Sensitivity analyses of the treatment effect using alternative models were consistent with the main analysis and ranged from a

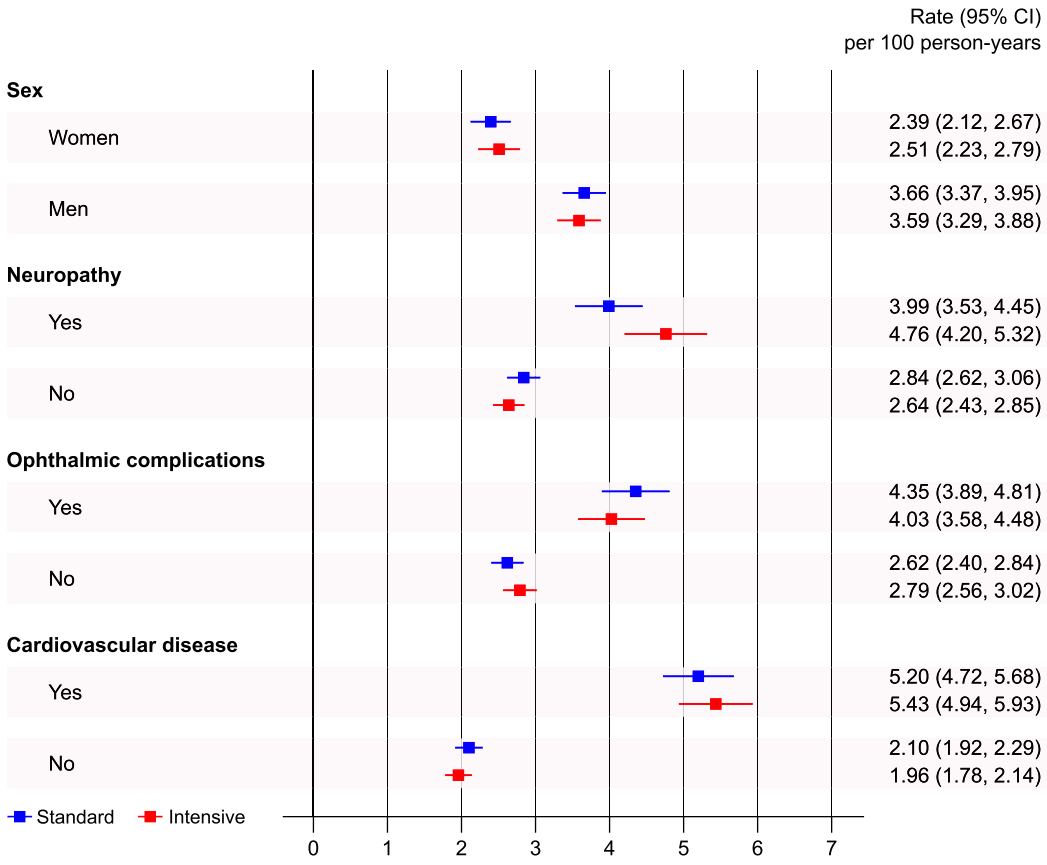

FIGURE 2 Rates of cardiovascular events and death by sex and baseline diabetes complications. Blue: standard treatment; red: intensive treatment. Spikes indicate 95% confidence intervals. The figure shows that for each baseline characteristic the rates in total cardiovascular events were very similar across treatment arms; however, within each treatment arm, these rates varied substantially across baseline characteristics, for example, increasing from 1.96 events in those without to 5.43 per 100 person-years in those with baseline cardiovascular disease in the intensive treatment arm.

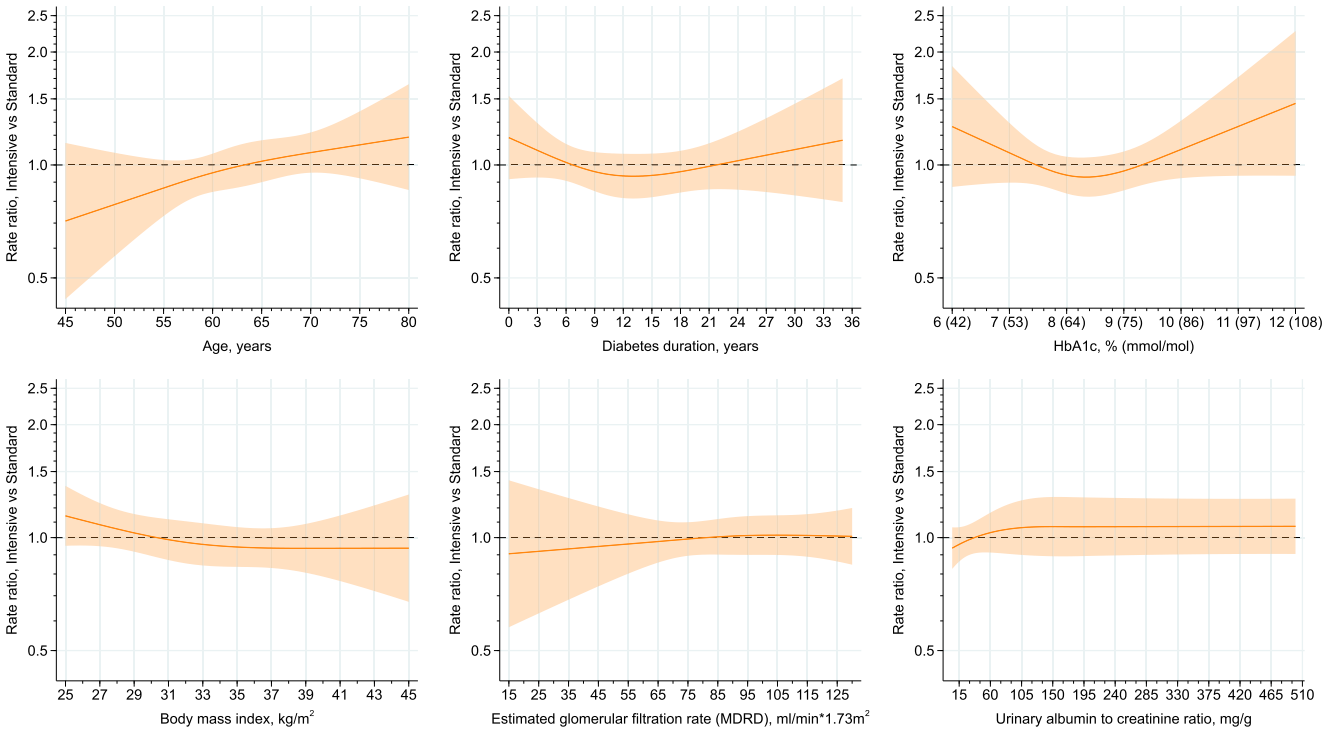

FIGURE 3 Treatment effect across baseline characteristics of patients. MDRD, Modification of Diet in Renal Disease. Shaded areas indicate 95% confidence intervals. There was little evidence for a difference in the treatment effect by baseline duration of diabetes, body mass index, estimated glomerular filtration rate, or urinary albumin to creatinine ratio, but some evidence for lower efficacy of intensive treatment with increasing age and greater efficacy with lower age and HbA1c values between 8% [64 mmol/mol] and 8.9% [74 mmol/mol].

hazard ratio of 0.98 (95% CI: 0.90, 1.07) with the Andersen-Gill model to a hazard ratio of 1.00 (0.92, 1.08) with the Prentice-Williams-Peterson Total Time model (Table S2).

4 | DISCUSSION

In this post-hoc analysis of the ACCORD and ACCORDION studies, there was no evidence of an effect of intensive glucose control in patients at high cardiovascular risk on the cumulative burden of macrovascular disease, defined as the total of the first occurrences of each MACE component, that is, non-fatal stroke, non-fatal myocardial infarction, hospitalisation for heart failure, and cardiovascular death. However, increasing age and extremes of HbA1c were associated with statistically non-significant changes in the treatment effect on the event rates, with a possible beneficial effect of intensive glucose-lowering therapy in younger patients who may be strongest in those with a baseline HbA1c below 7.0% (53 mmol/mol) and potential harm in older patients with a baseline HbA1c above 9.0 (75 mmol/mol). Irrespective of treatment, event rates were also increased in participants who were male, had pre-existing neuropathy or ophthalmic complications, or had a history of cardiovascular disease. In line with the drive towards individualised treatment in current guidelines, these results can help to define subgroups of patients in whom intensive glucose control may offer limited benefits or carry increased risks, or in whom the risk of macrovascular disease is associated with other easily identifiable characteristics regardless of treatment.[31]

These results are broadly in line with those of previous trials investigating the effects of intensive glucose control. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Administration Diabetes Trial (VADT), or their follow-up studies likewise found no effect or even a slight reduction of macrovascular events in intensively treated participants, while some long-term benefits from early treatment emerged in the UK Prospective Diabetes Study (UKPDS).[25,32–35] More specifically, our findings of possible higher benefit of intensive glucose control in younger patients with a low baseline HbA1c tally well with a previous post-hoc analysis of the ACCORD, which adopted machine learning methods to show an absolute mortality risk decrease of 2.3% in patients with a low haemoglobin glycosylation index (<0.44), absence of obesity (BMI<30 kg/m^2), and younger age (<61 years).[8]

However, our study also contrasts subgroup-analyses of VADT, which identified benefits from intensive glucose control in patients without radiologically evident coronary artery calcification and those with a shorter duration of diabetes.[36,37] Further, they do not confirm results from a meta-analysis of ACCORD, ADVANCE, UKPDS and VADT that found greater benefits from intensive glucose control in patients without compared to those with a history of macrovascular disease at baseline.[38] While these studies reflect current guidelines cautioning that stringent glucose goals

might be harmful for patients with longer duration of type 2 diabetes or established cardiovascular disease, the present analysis did not find evidence for increased harm in these patient subgroups, even though these characteristics are risk factors for macrovascular complications.[31]

A recurrent events analysis shifts the perspective away from a binary view of macrovascular complications in type 2 diabetes, which considers only the presence or absence of baseline cardiovascular disease and the occurrence of a single major cardiovascular event thereafter. Instead, it better captures the natural history of both type 2 diabetes and cardiovascular disease, which are characterised by continuous progression and acute events that contribute to a total burden of disease. As we have shown, considering more than a single event can generate novel insights and call into question orthodoxies derived from the binary understanding of cardiovascular disease inherent in trials on intensive glucose control.

Operationalising such an approach comes with some challenges common to trials adopting a primary composite outcome of MACE. For one in time-to-first event analyses, classically each component of the primary composite MACE is given the same status from an analytical perspective. Similarly, when estimating the total disease burden in our analysis, equal importance was given to each outcome investigated in our study; for example, non-fatal myocardial infarction and death from cardiovascular causes were treated the same. Likewise, the value of individual components of MACE, and the use of MACE to capture the heterogeneous effects of treatments are subject to continuing debate.[11,39] While recurrent events analyses of single components should therefore be essential in any trial using a composite endpoint, the total disease burden captured in a given study is necessarily context-dependent, mirroring difficulties in comparing study results due to different patient populations.

Our study has several limitations. Firstly, we were only able to account for the first event of each type, as further events of the same type were not recoded in the ACCORD or ACCORDION studies. Since recurrent events of the same type may reflect the progression of a disease process, such as atherosclerosis, which could increase the risk of other event types including mortality, and since each event is clinically relevant in its own right, such additional data would help to confirm and expand the conclusions of this analysis. Our study is also subject to a number of limitations inherent in post-hoc analyses of the ACCORD and ACCORDION. These include the relatively short duration of intensive treatment, the high risk of cardiovascular disease of the participants, the lack of other important outcomes such as total hospitalisation and microvascular end-points, and the absence of novel glucose-lowering agents. Based on these limitations, we would recommend future trials or post-hoc analyses to consider the role of intensive glycaemic therapy within a wider patient population, utilise the full spectrum of available agents in assessing the value of glycaemic targets, and adopt a recurrent-events perspective for individual and composite outcomes from the point of study design.

In conclusion, re-analysis of all available events from ACCORD and ACCORDION shows no increase in the risk of macrovascular complications with intensive glucose therapy, and points towards differential treatment effects in patients at the extremes of age and HbA1c. This increases the confidence in the existence of readily identifiable patient subgroups in whom intensive glucose treatment may increase or reduce the risk of both the first and subsequent cardiovascular events. The data also suggest that certain patient characteristics are associated with an increased risk of these complications regardless of treatment. Lastly, this study underlines the need to shift the perspective away from first events towards the total burden of disease to better reflect the natural history of diabetes and complications. It also cautions that, despite intense investigation, our understanding of the value of intensive glucose control in type 2 diabetes is likely to remain incomplete until such methodological aspects have been addressed.

AUTHOR CONTRIBUTIONS

Study idea: Francesco Zaccardi; study design and protocol: David E. Kloecker, Francesco Zaccardi; data preparation and analysis: David E. Kloecker, Francesco Zaccardi; first draft: David E. Kloecker, Francesco Zaccardi; study critical revision and manuscript draft: all Authors.

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CONFLICTS OF INTEREST STATEMENT

David E. Kloecker: No relevant conflict of interests related to this research. Melanie J. Davies: has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, as advisory board member for Servier and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi–Aventis, Lilly, Boehringer Ingelheim and Janssen. DP: No relevant conflict of interests related to this research. Kamlesh Khunti: has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi–Aventis, Lilly and Merck Sharp & Dohme; has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi–Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme; and has received funds for research and served on advisory boards for Lilly, Sanofi–Aventis, Merck Sharp & Dohme and Novo Nordisk. Francesco Zaccardi: has received grants in support of investigator-initiated studies from Novo Nordisk, Sanofi–Aventis, Boehringer Ingelheim, Merck Sharp & Dohme, AstraZeneca, and Servier; and speaker fees from Napp Pharmaceuticals and Boehringer Ingelheim.

DATA AVAILABILITY STATEMENT

ACCORD and ACCORDION data are available at https://biolincc.nhlbi.nih.gov/studies/accord/. The study protocol and statistical code are available on request from the corresponding author David Kloecker.

ETHICS STATEMENT

Ethical approval for the current study was granted by the University of Leicester Ethics Review board (application 12192).

STUDY REGISTRATION

#7556 - ACCORD_epi_analysis (28 April 2020).

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3634.

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SUPPORTING INFORMATION

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