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The comparative effects of intensive glucose lowering in diabetes patients aged below or above 65 years: results from the ADVANCE trial

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Abstract

Aims: For relatively old patients with diabetes, current guidelines recommend adjustment of glycaemic goals based on patients' cognitive function, or coexisting chronic illnesses. However, the evidence which supports the efficacy and safety of intensive glucose lowering in older patients with diabetes is scarce.

Materials and methods: The effects of intensive glucose lowering (to a target HbA_{1c} of ≤6.5%) on major clinical outcomes were evaluated by Cox regression models according to subgroups defined by baseline age of <65 or ≥65 years in the ADVANCE trial (n = 11,140).

Results:

Over a median follow-up of 5 years, intensive glucose lowering significantly decreased the risk of the composite of major macrovascular and microvascular events (hazard ratio 0.90, 95% CI 0.82-0.98), with no heterogeneity in the effects across age subgroups (p for heterogeneity=0.44). Relative effects on all-cause death, cardiovascular death, and components of major vascular events were also similar (p for heterogeneity ≥0.06), except for severe hypoglycaemia, of greater risk for patients <65 years. Absolute benefits and harms were broadly consistent across subgroups. Among patients aged ≥65 years, randomised treatment effects did not differ significantly across different levels of cognitive function or coexisting chronic illnesses.

Conclusions: Our results suggest that an intensive glycaemic control strategy to reduce HbA_{1c} to 6.5% provided broadly similar benefits and harms and may be recommended for older, as well as younger, patients.

Clinical trial registration number: NCT00145925, ClinicalTrials.gov

Introduction

Along with worldwide population aging, the number of elderly patients with diabetes has been growing. In 2019, one in five diabetes patients were reported to be aged 65 or more (136 million patients).[1] The number of patients with diabetes over 65 years old is expected to further increase to 195 million by 2020, and to 276 million by 2045.[1] Older patients with diabetes have been shown to be at greater risk of premature death, as well as cardiovascular events, compared with younger patients.[2] In addition to the deleterious impacts of diabetic complications on each patient's prognosis, the increase in diabetes patients in an aging society will impose massive burdens on public health systems and health finances.[1] Therefore, preventing incidence and progression of these events in older patients is crucial.

Glycaemic control has long been an essential part of diabetes care, to reduce or slow the risk of long-term diabetic complications.[3] Generally, a HbA_{1c} level of less than 7% is recommended to prevent complications for nonpregnant adults with diabetes,[3] whereas for older patients, current guidelines of the American Diabetes Association recommend to adjust glycaemic goals based on patients' cognitive function, coexisting chronic illnesses, or functional status.[3] However, the evidence which supports the efficacy and safety of intensive glucose lowering and the individualization of glycaemic target according to their characteristics is scarce.

The objective of the present study was to compare the efficacy and safety of intensive glucose lowering in patients with type 2 diabetes stratified by age (<65 and ≥ 65 years), and examine whether the effects differ according to patients' characteristics in the older patient group.

Materials and Methods

Study design and population

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a factorial randomised controlled trial conducted by 215 centres in 20 countries to examine the effects on vascular outcomes of intensive blood glucose lowering and blood pressure lowering in patients with type 2 diabetes (ClinicalTrials.gov number, NCT00145925).[4-6] Shortly, a total of 11,140 individuals with type 2 diabetes at high risk of cardiovascular events were randomised to either a gliclazide (modified release)-based intensive glucose control aiming for a HbA_{1c} level ≤6.5% or standard glucose control on the basis of local guideline, and also randomised to either a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) or matching placebo after a 6-week run-in period, during which usual methods of glucose control were continued, and perindopril and indapamide in a fixed combination were given. Doses of glucose-control treatment during the trial were at the discretion of the treating physician. Doses of randomised perindopril and indapamide treatment were doubled to 4 mg for perindopril and 1.25 mg for indapamide after 3 months. A median of follow-up duration was 5.0 years. Ethics approval for the trial was obtained from institutional review board of each centre, and all participants provided written informed consent.

Demographic and clinical variables

Participants were classified into 2 groups: age <65 and ≥65 years. Cognitive function was evaluated by the Mini Mental State Examination (MMSE) at baseline (before randomisation), at 2 yearly intervals during follow-up, and at study completion. Participants were classified into 'normal' for baseline MMSE scores of ≥28, "mild dysfunction" for those of 24-27, and "severe dysfunction" for those ≤23.[7] Chronic illness was defined as conditions serious enough to require medications or lifestyle management,[3] and the present study included history of heart failure, currently treated hypertension, estimated glomerular filtration rate <60 ml/min/1.73m^2, history of myocardial infarction, and history of stroke.

Outcomes

The outcomes examined in the present analysis were incidence of 1) the composite of major macrovascular (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular (new or worsening nephropathy or retinopathy) events, 2) all-cause death, 3) cardiovascular death, 4) major macrovascular events, 5) major coronary events, 6) major cerebrovascular events, 7) major microvascular events, 8) new or worsening nephropathy, 7) new or worsening retinopathy, and 8) severe hypoglycaemia, as previously described [6]. A composite of dementia and cognitive decline was also assessed. Dementia was defined by criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, and cognitive decline was defined as a decrease of at least 3 points in the Mini Mental State Examination score.[6,8]

Statistical analysis

Differences in baseline characteristics between subgroups defined by baseline age were tested by t tests or χ^2 tests, as appropriate. The effects of randomised treatment on outcomes were evaluated by unadjusted Cox regression models across the age subgroups, and tested by adding interaction terms to the models. We performed sensitivity analyses, in which participants aged ≥65 were further split into those aged 65-74, and ≥75 years. Additional analyses were also conducted in those aged ≥65 years, divided according to cognitive function (MMSE, ≥28, 24-27, and ≤23) and by number of coexisting chronic illnesses (≤1, and ≥2). The absolute effects of intensive glucose-lowering on the outcomes were also assessed. Incidence rates per thousand person years by randomised treatment allocation, and their differences (absolute risk reductions) were computed by using Poisson regression models. The differences in the absolute risk reductions between age subgroups were subsequently calculated. Statistical analyses were performed with SAS 7.11 (SAS Institute, Cary NC, USA) and Stata software (release 13, StataCorp, College Station, TX). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Of 11,140 participants included in the ADVANCE trial, 6,613 (59%) were aged ≥65 years at baseline (Table 1). These older participants were more likely to have longer diabetes duration, have higher systolic BP, HDL cholesterol levels, and lower diastolic BP, HbA_{1c}, LDL cholesterol, triglyceride, BMI, and eGFR levels, in comparison with younger participants (all p <0.001). The proportion of participants with a history of macrovascular disease or those treated with metformin were less frequent in the older participants (all p <0.001). Baseline characteristics between randomised blood glucose lowering treatment were generally well balanced within each age category (Supplementary Table 1).

Randomised treatment effects of intensive glucose-control according to age

Overall, intensive glucose-lowering was significantly associated with a decreased risk of the composite of major macrovascular and microvascular events (hazard ratio [HR] 0.90, 95% CI 0.82-0.98, Figure 1). The effects were consistent regardless of subgroups defined by age (p for heterogeneity=0.44); the HRs for intensive glucose-lowering in comparison with standard control were 0.86 (95% CI: 0.75-0.99) in participants aged <65 years and 0.92 (0.83-1.03) in those aged ≥65 years. The effects of intensive glucose-lowering were also consistent across subgroups defined by age for all-cause death, cardiovascular death, major macrovascular events, major coronary events, major cerebrovascular events, major microvascular events and new or worsening nephropathy ($p \geq 0.11$) although there was some indication of heterogeneity for new or worsening retinopathy ($p=0.06$). Intensive glucose-lowering significantly increased the risk of severe hypoglycaemia (HR 1.86, 95% CI 1.42-2.44), with greater risk in the younger patients (p for heterogeneity=0.02). The effects on cognitive function (combined dementia and cognitive decline) did not differ significantly across age subgroups (p for heterogeneity=0.46). Sensitivity analyses which accounted for competing risk of death provided almost identical results (Supplementary Table 2). Broadly similar findings were observed in sensitivity analyses when participants aged ≥65 years were further split into those with 65-74 (n=5,605) and ≥75 years (n=1,008) (Supplementary Figure 1). The consistency of the treatment effects did not change substantially when linear trends across subgroups were examined ($p \geq 0.10$), with the exception of new or worsening retinopathy and severe hypoglycaemia (p=0.06 and 0.02, respectively). Additional subgroup analyses by baseline presence of vascular disease (either macrovascular or microvascular) and region of residence showed no evidence of heterogeneity in the association between the effects of intensive glucose lowering and age (Supplementary Figure 2 and 3, $p \geq 0.09$), with the only exceptions of combined macrovascular and microvascular events and major macrovascular events in subgroup analyses by region (p=0.02 and 0.01, Supplementary Figure 3).

Risk reductions according to age

In terms of the absolute risk reductions, the benefits or harms associated with intensive glucose lowering were generally similar between younger and older patients (Figure 2; p for heterogeneity ≥0.06), with the sole exception of new or worsening of retinopathy (p for heterogeneity=0.047). Although there were no significant differences, the absolute benefit was greatest for all-cause mortality; the number needed to treat to prevent one death over 5 years was 258 for those aged <65 years, and 124 for those aged ≥65 years. Similar tendencies were observed for cardiovascular death, major macrovascular events, major coronary events, and new or worsening nephropathy.

Cognitive function and coexisting chronic illnesses in patients aged ≥65 years

In patients aged ≥65 years, the effects of intensive glucose lowering were consistent across different levels of cognitive function (Figure 3; p for heterogeneity ≥0.10) or coexisting chronic illnesses (Supplementary Figure 4; p for heterogeneity ≥0.39).

Discussion

The present analysis showed that the effects of intensive glucose lowering on death and vascular events in participants with type 2 diabetes were consistent irrespective of whether patients were less than 65 years or not. Furthermore, the excess risk of severe hypoglycaemia associated with intensive glucose lowering was smaller in the older participants. In addition, the absolute benefits of intensive glucose lowering tended to be greater in older patients for several outcomes, including all-cause and cardiovascular death. These effects were not modified by participants' cognitive function or coexisting chronic illnesses. Our results suggest that the benefits of intensive glucose-lowering may outweigh the risks, irrespective of age.

The standard glycaemic target is currently recommended to be modified and relaxed in older patients, given their vulnerability to hypoglycaemia and its adverse consequences. However, few studies have examined the benefits and harms of intensive glucose lowering in older patients with diabetes. Previous findings from the ACCORD trial showed that effects of intensive glucose lowering on cardiovascular outcomes were consistent between patients aged

≥65 years or younger, with the exception of cardiovascular and all-cause mortality.[9] Intensive glycaemic control was associated with an increased risk of cardiovascular and all-cause mortality in younger patients, whereas no such association was observed for older patients.[9] On the other hand, the current report from the ADVANCE trial shows that treatment effects associated with intensive glucose lowering reduce the proportionate risk of vascular events and mortality, to a similar extent, irrespective of age subgroups (<65 and ≥65 years). The reason for the observed discrepancies is unclear, but one possible explanation may be the relatively smaller increase in the risk of severe hypoglycaemia in older patients in the ADVANCE trial (HR [95% CIs], ≥65 years: 1.53 [1.12, 2.08], <65 years: 3.43 [1.89, 6.22], p for heterogeneity=0.02). The ACCORD trial found no such difference (HR [95% CIs], ≥65 years: 2.93 [2.31, 3.73], <65 years: 2.94 [2.34, 3.69]).[9] Severe hypoglycaemia increases the risk of premature death[10,11] and cardiovascular events.[10] Differences in characteristics of the study populations, particularly the longer duration of diabetes in patients in ACCORD (10.9 years) [12] than in ADVANCE (7.9 years), and different approaches, and intervention targets, to glycaemic control[13] may also have played a role.

We found that intensive glucose lowering reduced the risk of clinical outcomes irrespective of age, both in relative and absolute terms. The absolute benefits and harms were broadly similar between younger and older patients, which is a novel finding, although the magnitudes of the risk difference were modest. Assessments of absolute risks provide more clinically relevant information for making decisions in daily practice, as they provide the expected number of patients who will avoid experiencing the outcomes by use of the intervention.[14,15]

In addition to the advice to set different glycaemic goals for older patients (HbA_{1c} <7.5%) from those of younger patients (HbA_{1c} <7.0%), further relaxation of target levels by patients' characteristics/health status is also recommended.[3] Much less-stringent glycaemic goals, such as HbA_{1c} <8.0-8.5%, are recommended if patients have coexisting chronic illnesses, cognitive impairment or reduced functionality,[3] as they are not likely to gain benefits from glucose lowering but are rather likely to suffer from serious adverse outcomes such as hypoglycaemia. However, to date few studies have examined the efficacy and safety of this strategy. To validate the current recommendation, we conducted additional analyses according to cognitive function or coexisting chronic illnesses in patients aged ≥65 years. Importantly, there was no evidence of heterogeneity in the effects of randomised intensive glucose control treatment on the risk of clinical outcomes assessed across subgroups defined by cognitive function or coexisting chronic illnesses. To the best of our knowledge, this is the first study to demonstrate the consistent treatment effects of intensive glucose lowering across subgroups defined by functional status recommended to be considered to set glycaemic goals in older patients. Taken together, tight glycaemic control may be beneficial in older patients as well as in younger patients with diabetes, although close attention to the risk of severe hypoglycaemia is needed.

For the past decade, new drug classes with established cardio-renal benefits and low risk of hypoglycaemia, such as sodium–glucose co-transporter 2 inhibitors[16,17] or glucagon-like peptide 1 receptor agonists,[18,19] have become available. These advancements in hypoglycaemic agents may enable us to achieve near-normal glycaemic targets more safely even in older patients. Further clinical trials are required to clarify the efficacy and safety of glycaemic intensification in older patients with diabetes by using the existing drug classes as well as those that do not increase hypoglycaemia.

The strengths of the present study include the large sample size enrolled from an international, multi-centre randomised controlled trial, the rigorous adjudication of major clinical outcomes including severe hypoglycaemia, and the large number of older participants, which allowed us to conduct the subgroup analyses. In addition, this is the first study evaluating treatment effects of intensive glucose lowering with stratification by comorbidities, cognitive function or functional status in older patients. However, the study also had some limitations. First, the participants consisted of those eligible for the randomised trial who were at high risk of cardiovascular events, and thus the applicability of the results to broader unselected populations may be limited. However, we have previously shown that the ADVANCE cohort is broadly typical of diabetes patients in community settings.[20] Second, the relatively small number of events among patients with ≥75 years or MMSE scores of 24-27 or ≤23 may be insufficient to establish the treatment effects in much older patients or older patients with cognitive impairment. Further studies are needed to examine the effects of intensive glucose control in such patients. Third, the effects of intensive glucose lowering on other relevant outcomes, such as quality of life and cost of treatment, were not assessed in the present study. Fourth, the ADVANCE trial was conducted in the late 2000s, and thus the background care of diabetes may not reflect contemporary care with new drug classes, as mentioned above. Fifth, this study was a post-hoc analyses of the ADVANCE trial, which was not originally designed to examine the effects of intensive glucose lowering in each age category. However, baseline characteristics of participants randomly assigned to intensive and standard control groups were mostly similar within each age subgroups. Therefore, we believe that our comparisons of the randomised effects between age categories will be robust. Sixth, significant interaction observed in the present study may be due to a chance finding following a number of statistical tests conducted.

In conclusion, our results demonstrated that the randomised treatment effects of tight glycaemic intensification on the long-term risk of major clinical outcomes were similar among patients aged <65 and ≥65 years. In addition, there was no significant heterogeneity in the effects across subgroups stratified according to comorbidities, or cognitive function. These findings suggest that an intensive glycaemic control strategy may be beneficial for patients aged 65 years or more with type 2 diabetes as well as in younger patients, with close attention to the incidence of hypoglycaemia.

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Conflict of Interest

TO reports no conflicts of interest. JC received research grants from the National Health and Medical Research Council of Australia and from Servier for the ADVANCE trial and ADVANCE-ON post-trial follow-up, and honoraria for speaking about these studies at scientific meetings, and reports grant support from Program Grant APP1149987 from the National Health and Medical Research Council of Australia. MC reports grants from Novo Nordisk, grants and personal fees from Boehringer Ingelheim, and personal fees from Servier, AstraZeneca, Novartis, Merck, and Bayer, outside the submitted work. PH reports consulting fees from Servier, grant support from Quebec CQDM and Servier. SH reports grants from the George Institute for Global Health, during the conduct of the study; other from Servier, outside the submitted work. MM received personal fees from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme, Abbott, Novartis, Servier, and AstraZeneca and grant support from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme and Novartis. GM reports personal fees from Servier Laboratories, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini Group, Recordati, and Takeda Pharmaceutical Company. NP received honoraria and personal fees from Servier Laboratories, Takeda Pharmaceutical Company, Menarini Group, and Pfizer, grant support from Servier Laboratories, and Pfizer. MW reports consultancy fees

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Author contributions

TO had the initial idea for this study, conducted statistical analysis with advice from MW, and drafted the manuscript. JC and MW helped design the study and draft the manuscript. All authors contributed to discussion and reviewed and edited the manuscript. JC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edition. www.diabetesatlas.org (accessed November 14, 2019).

2. Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia.* 2014;57(12):2465-2474.

3. American Diabetes Association. Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S1-S204.

4. ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. *Diabetologia.* 2001;44(9):1118-1120.

5. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007;370(9590):829-840.

6. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.

7. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA.* 1993;269(18):2386-2391.

8. Batty GD, Li Q, Huxley R, et al. Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the Action in Diabetes and

Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. *Eur Psychiatry.* 2013;28(1):49-52.

9. Miller ME, Williamson JD, Gerstein HC, et al. Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD Trial. *Diabetes Care.* 2014;37(3):634-643.
10. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med.* 2010;363(15):1410-1418.
11. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ.* 2010;340:b4909.
12. Papademetriou V, Lovato L, Doumas M, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int.* 2015;87(3):649-659.
13. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia.* 2009;52(11):2288-2298.
14. Woodward M. Epidemiology: Study Design and Data Analysis. Boca Raton, Florida, Chapman & Hall/CRC, 2014.
15. Woodward M. Rationale and tutorial for analysing and reporting sex differences in cardiovascular associations. *Heart.* 2019;105(22):1701-1708.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

17. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-657.

18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.

19. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-1844.

20. Chalmers J, Arima H. Importance of blood pressure lowering in type 2 diabetes: focus on ADVANCE. *J Cardiovasc Pharmacol.* 2010;55(4):340-347.

Table 1. Baseline characteristics of study participants according to age

	Age (years)		
Variable	<65	≥65	P value
Number of participants	4,527	6,613	
Age (years)	59 (3)	70 (4)	<0.001
Female (%)	1,954 (43.2)	2,779 (42.0)	0.23
Residence in Asia (%)	1,947 (43.0)	2,189 (33.1)	<0.001
Duration of diabetes mellitus (years)	7.6 (5.9)	8.1 (6.6)	<0.001
History of macrovascular disease (%)	1,574 (34.8)	2,016 (30.5)	<0.001
History of myocardial infarction (%)	547 (12.1)	787 (11.9)	0.77
History of stroke (%)	425 (9.4)	598 (9.0)	0.54
History of heart failure (%)	135 (3.0)	221 (3.3)	0.29
History of microvascular disease (%)	491 (10.9)	664 (10.0)	0.17
Currently treated hypertension (%)	3,073 (67.9)	4,582 (69.3)	0.12
Systolic BP (mmHg)	142 (21)	147 (22)	<0.001
Diastolic BP (mmHg)	82 (11)	80 (11)	<0.001
Current smoking (%)	1,073 (23.7)	609 (9.2)	<0.001
HbA_{1c} (%)	7.7 (1.7)	7.4 (1.5)	<0.001
(mmol/mol)	60.1 (18.1)	57.4 (16.1)	
Blood glucose-lowering treatments			
Gliclazide (modified release)† (%)	369 (8.2)	496 (7.5)	0.21
Other sulfonylurea (%)	2,864 (63.3)	4,227 (63.9)	0.49
Metformin (%)	2,906 (64.2)	3,846 (58.2)	<0.001
Thiazolidinedione (%)	185 (4.1)	222 (3.4)	0.04
α-glucosidase inhibitor (%)	381 (8.4)	579 (8.8)	0.53
Glinide (%)	92 (2.0)	95 (1.4)	0.02
Any oral hypoglycaemic agents† (%)	4,170 (92.1)	5,959 (90.1)	<0.001
Insulin (%)	68 (1.5)	91 (1.4)	0.58
LDL cholesterol (mmol/l)	3.2 (1.1)	3.1 (1.0)	<0.001
HDL cholesterol (mmol/l)	1.2 (0.4)	1.3 (0.3)	<0.001

Triglycerides (mmol/l)	1.8 (1.3, 2.5)	1.6 (1.1, 2.2)	<0.001
Body mass index (kg/m^2)	28.8 (5.6)	28.0 (4.9)	<0.001
eGFR (ml/min/1.73m^2)	81 (17)	70 (17)	<0.001
Randomized treatments			
Intensive blood glucose control (%)	2,275 (50.3)	3,296 (49.8)	0.67
Perindopril-indapamide (%)	2,251 (49.7)	3,318 (50.2)	0.64

Values shown are means (SDs) for continuous variables, except for triglycerides, where medians (interquartile intervals) are given, and numbers (percentages) for categorical variables.

† Randomised treatment with gliclazide was not included.

Abbreviations: BP, blood pressure, eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure legends

Figure 1. Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline age.

White diamonds indicate the HRs for subgroups defined by baseline age.

Black diamonds indicate the HRs of overall for participants of the ADVANCE trial (n = 11,140).

Participants with baseline MMSE values were included for the analyses of combined dementia and cognitive decline (n=11,132).

Abbreviations: CI, confidence interval.

Figure 2. Comparison of the absolute risk reductions on major clinical outcomes according to baseline age.

White diamonds indicate the absolute risk reductions for subgroups defined by baseline age.

Black diamonds indicate the absolute risk reductions of overall for participants of the ADVANCE trial (n = 11,140).

Participants with baseline MMSE values were included for the analyses of combined dementia and cognitive decline (n=11,132).

Abbreviations: CI, confidence interval; NNT, number needed to treat; PYs, person-years.

Figure 3. Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline cognitive function in participants aged 65 or more.

White diamonds indicate the HRs for subgroups defined by baseline MMSE values.

Black diamonds indicate the HRs of overall for participants aged 65 or more (n=6,613).

Participants with baseline MMSE values were included for the analyses of combined dementia and cognitive decline (n=6,607).

Abbreviations: CI, confidence interval; MMSE, the Mini Mental State Examination.

Figure 1

Age groups (years)	N of events (%) Intensive	Standard	Hazard ratio (95% CI)	P for heterogeneity
Combined major macrovascular and microvascular events				
<65	367 (16.1)	421 (18.7)	0.86 (0.75, 0.99)	0.44
≥65	642 (19.5)	695 (21.0)	0.92 (0.83, 1.03)	
Overall	1009 (18.1)	1116 (20.0)	**0.90 (0.82, 0.98)**	
All-cause death				
<65	111 (4.9)	119 (5.3)	0.93 (0.72, 1.20)	0.95
≥65	387 (11.7)	414 (12.5)	0.94 (0.82, 1.08)	
Overall	498 (8.9)	533 (9.6)	**0.94 (0.83, 1.06)**	
Cardiovascular death				
<65	63 (2.8)	64 (2.8)	0.98 (0.69, 1.39)	0.48
≥65	190 (5.8)	225 (6.8)	0.85 (0.70, 1.03)	
Overall	253 (4.5)	289 (5.2)	**0.88 (0.74, 1.04)**	
Major macrovascular events				
<65	165 (7.3)	165 (7.3)	0.99 (0.80, 1.23)	0.59
≥65	392 (11.9)	425 (12.8)	0.93 (0.81, 1.06)	
Overall	557 (10.0)	590 (10.6)	**0.94 (0.84, 1.06)**	
Major coronary events				
<65	94 (4.1)	83 (3.7)	1.13 (0.84, 1.52)	0.11
≥65	216 (6.6)	254 (7.7)	0.85 (0.71, 1.02)	
Overall	310 (5.6)	337 (6.1)	**0.92 (0.79, 1.07)**	
Major cerebrovascular events				
<65	66 (2.9)	84 (3.7)	0.78 (0.56, 1.07)	0.11
≥65	172 (5.2)	162 (4.9)	1.07 (0.86, 1.32)	
Overall	238 (4.3)	246 (4.4)	**0.97 (0.81, 1.16)**	
Major microvascular events				
<65	235 (10.3)	282 (12.5)	0.82 (0.69, 0.98)	0.47
≥65	291 (8.8)	323 (9.7)	0.90 (0.77, 1.05)	
Overall	526 (9.4)	605 (10.9)	**0.87 (0.77, 0.97)**	
New or worsening nephropathy				
<65	105 (4.6)	123 (5.5)	0.85 (0.66, 1.10)	0.41
≥65	125 (3.8)	169 (5.1)	0.74 (0.58, 0.93)	
Overall	230 (4.1)	292 (5.2)	**0.79 (0.66, 0.93)**	
New or worsening retinopathy				
<65	151 (6.6)	183 (8.1)	0.82 (0.66, 1.01)	0.06
≥65	181 (5.5)	166 (5.0)	1.09 (0.89, 1.35)	
Overall	332 (6.0)	349 (6.3)	**0.95 (0.82, 1.10)**	
Severe hypoglycaemia				
<65	48 (2.1)	14 (0.6)	3.43 (1.89, 6.22)	0.02
≥65	102 (3.1)	67 (2.0)	1.53 (1.12, 2.08)	
Overall	150 (2.7)	81 (1.5)	**1.86 (1.42, 2.44)**	
Combined dementia and cognitive decline				
<65	274 (12.0)	292 (13.0)	0.94 (0.79, 1.10)	0.46
≥65	634 (19.3)	627 (18.9)	1.01 (0.90, 1.12)	
Overall	908 (16.3)	919 (16.5)	**0.99 (0.90, 1.08)**	

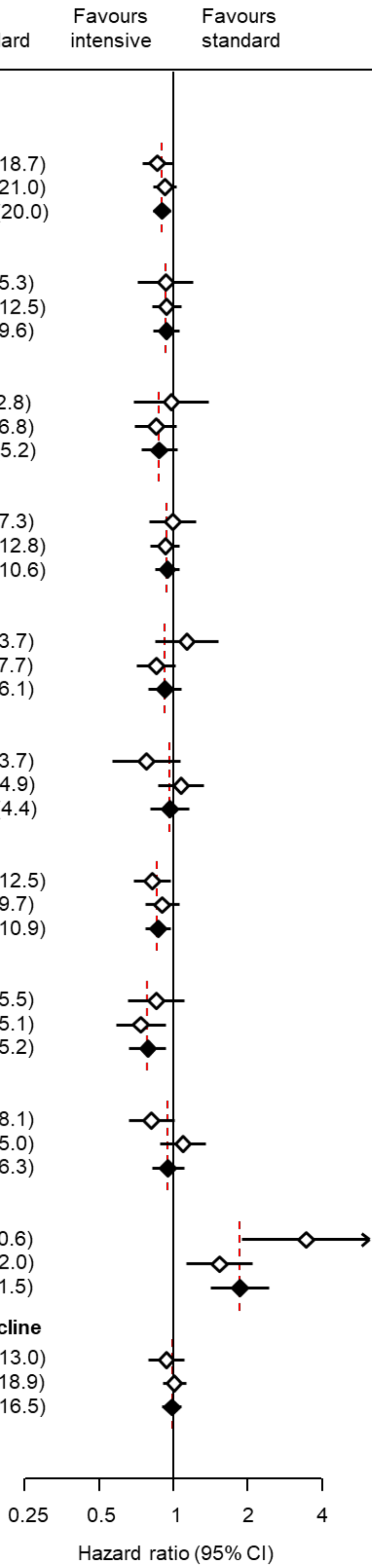

Figure 2

Age groups (years)	Incidence rate (per 1000 PYs) Intensive	Standard	Absolute risk difference per 1000 PYs (95% CIs)	P for heterogeneity	NNT to prevent one event over 5 years
Combined major macrovascular and microvascular events					
<65	35.6	41.5	-5.8 (-11.2, -0.5)	0.56	34
≥65	43.9	47.6	-3.7 (-8.6, 1.2)		54
Overall	**40.5**	**45.1**	**-4.6 (-8.2, -1.0)**		**43**
All-cause death					
<65	10.0	10.8	-0.8 (-3.5, 1.9)	0.71	258
≥65	24.7	26.3	-1.6 (-5.2, 1.9)		124
Overall	**18.6**	**19.9**	**-1.3 (-3.7, 1.1)**		**154**
Cardiovascular death					
<65	5.7	5.8	-0.1 (-2.1, 1.9)	0.21	1658
≥65	12.1	14.3	-2.2 (-4.7, 0.4)		92
Overall	**9.5**	**10.8**	**-1.4 (-3.1, 0.4)**		**149**
Major macrovascular events					
<65	15.3	15.4	-0.1 (-3.4, 3.2)	0.43	1741
≥65	25.9	28.0	-2.1 (-5.8, 1.6)		96
Overall	**21.5**	**22.8**	**-1.3 (-3.9, 1.3)**		**154**
Major coronary events					
<65	8.6	7.6	1.0 (-1.4, 3.4)	0.06	-205
≥65	14.0	16.4	-2.4 (-5.2, 0.3)		82
Overall	**11.8**	**12.8**	**-1.0 (-2.9, 0.9)**		**194**
Major cerebrovascular events					
<65	6.1	7.8	-1.7 (-3.9, 0.5)	0.14	116
≥65	11.2	10.5	0.7 (-1.6, 3.1)		-278
Overall	**9.1**	**9.4**	**-0.3 (-2.0, 1.3)**		**656**
Major microvascular events					
<65	22.3	27.1	-4.8 (-9.0, -0.5)	0.33	42
≥65	19.2	21.4	-2.1 (-5.3, 1.1)		94
Overall	**20.5**	**23.7**	**-3.2 (-5.8, -0.6)**		**62**
New or worsening nephropathy					
<65	9.7	11.4	-1.7 (-4.5, 1.0)	0.53	116
≥65	8.1	10.9	-2.8 (-5.0, -0.7)		70
Overall	**8.7**	**11.1**	**-2.4 (-4.1, -0.7)**		**84**
New or worsening retinopathy					
<65	14.1	17.3	-3.2 (-6.6, 0.2)	0.047	63
≥65	11.8	10.8	1.0 (-1.4, 3.4)		-196
Overall	**12.8**	**13.5**	**-0.7 (-2.7, 1.3)**		**291**
Severe hypoglycaemia					
<65	4.4	1.3	3.1 (1.7, 4.5)	0.46	-64
≥65	6.6	4.3	2.3 (0.6, 3.9)		-88
Overall	**5.7**	**3.1**	**2.6 (1.5, 3.8)**		**-76**
Combined dementia and cognitive decline					
<65	25.6	27.6	-2.0 (-6.4, 2.4)	0.42	99
≥65	42.8	42.2	0.6 (-4.1, 5.3)		-314
Overall	**35.6**	**36.1**	**-0.5 (-3.8, 2.8)**		**370**

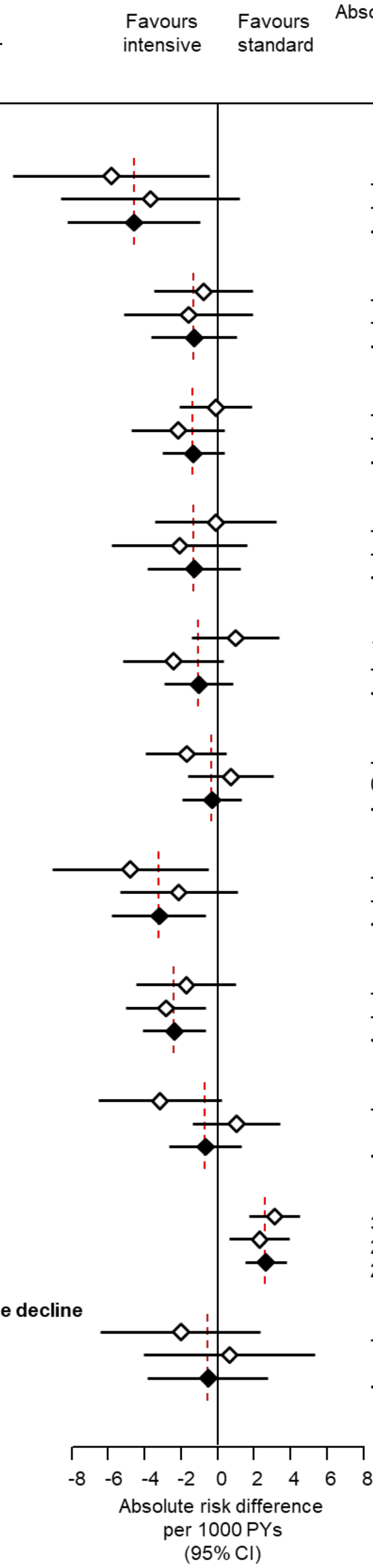

Figure 3

MMSE groups	N of events (%) Intensive	Standard	Hazard ratio (95% CI)	P for heterogeneity
Combined major macrovascular and microvascular events				
≥28	450 (18.5)	485 (19.4)	0.95 (0.83, 1.08)	0.68
24-27	169 (22.0)	190 (25.5)	0.85 (0.69, 1.05)	
≤23	23 (25.3)	20 (28.6)	0.87 (0.48, 1.58)	
Overall	642 (19.5)	695 (21.0)	**0.92 (0.83, 1.03)**	
All-cause death				
≥28	243 (10.0)	292 (11.7)	0.85 (0.72, 1.01)	0.21
24-27	124 (16.1)	108 (14.5)	1.12 (0.86, 1.44)	
≤23	19 (20.9)	14 (20.0)	1.05 (0.52, 2.09)	
Overall	387 (11.7)	414 (12.5)	**0.94 (0.82, 1.08)**	
Cardiovascular death				
≥28	116 (4.8)	148 (5.9)	0.80 (0.63, 1.02)	0.58
24-27	65 (8.5)	66 (8.9)	0.96 (0.68, 1.35)	
≤23	9 (9.9)	11 (15.7)	0.64 (0.27, 1.55)	
Overall	190 (5.8)	225 (6.8)	**0.85 (0.70, 1.03)**	
Major macrovascular events				
≥28	257 (10.6)	285 (11.4)	0.92 (0.78, 1.09)	0.64
24-27	119 (15.5)	112 (16.4)	0.95 (0.74, 1.22)	
≤23	16 (17.6)	18 (25.7)	0.66 (0.33, 1.29)	
Overall	392 (11.9)	425 (12.8)	**0.93 (0.81, 1.06)**	
Major coronary events				
≥28	141 (5.8)	175 (7.0)	0.82 (0.66, 1.03)	0.85
24-27	66 (8.6)	70 (9.4)	0.92 (0.65, 1.28)	
≤23	9 (9.9)	9 (12.9)	0.76 (0.30, 1.91)	
Overall	216 (6.6)	254 (7.7)	**0.85 (0.71, 1.02)**	
Major cerebrovascular events				
≥28	115 (4.7)	106 (4.2)	1.11 (0.85, 1.45)	0.37
24-27	51 (6.6)	47 (6.3)	1.06 (0.71, 1.57)	
≤23	6 (6.6)	9 (12.9)	0.47 (0.17, 1.35)	
Overall	172 (5.2)	162 (4.9)	**1.07 (0.86, 1.32)**	
Major microvascular events				
≥28	217 (8.9)	236 (9.4)	0.94 (0.78, 1.13)	0.23
24-27	66 (8.6)	84 (11.3)	0.75 (0.54, 1.03)	
≤23	8 (8.8)	3 (4.3)	2.11 (0.56, 7.96)	
Overall	291 (8.8)	323 (9.7)	**0.90 (0.77, 1.05)**	
New or worsening nephropathy				
≥28	100 (4.1)	121 (4.8)	0.84 (0.64, 1.09)	0.10
24-27	22 (2.9)	46 (6.2)	0.45 (0.27, 0.76)	
≤23	3 (3.3)	2 (2.9)	1.19 (0.20, 7.11)	
Overall	125 (3.8)	169 (5.1)	**0.74 (0.58, 0.93)**	
New or worsening retinopathy				
≥28	129 (5.3)	124 (5.0)	1.06 (0.83, 1.36)	0.75
24-27	47 (6.1)	40 (5.4)	1.14 (0.75, 1.74)	
≤23	5 (5.5)	2 (2.9)	1.97 (0.38, 10.17)	
Overall	181 (5.5)	166 (5.0)	**1.09 (0.89, 1.35)**	
Severe hypoglycaemia				
≥28	65 (2.7)	50 (2.0)	1.33 (0.92, 1.92)	0.30
24-27	31 (4.0)	13 (1.7)	2.33 (1.22, 4.46)	
≤23	6 (6.6)	4 (5.7)	0.96 (0.26, 3.57)	
Overall	102 (3.1)	67 (2.0)	**1.53 (1.12, 2.08)**	
Combined dementia and cognitive decline				
≥28	464 (19.1)	466 (18.6)	1.00 (0.88, 1.14)	0.97
24-27	144 (18.8)	142 (19.1)	0.99 (0.78, 1.24)	
≤23	26 (28.6)	19 (27.1)	1.11 (0.61, 2.00)	
Overall	634 (19.3)	627 (18.9)	**1.01 (0.90, 1.12)**