ARTICLE

Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial

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Abstract

Aims/hypothesis The relationship between cognitive function, cardiovascular disease and premature death is not well established in patients with type 2 diabetes. We assessed the effects of cognitive function in 11,140 patients with type 2 diabetes who participated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Furthermore, we tested whether level of cognitive function altered the beneficial effects of the BP-lowering and glycaemic-control regimens in the trial.

Methods Cognitive function was assessed using the Mini Mental State Examination at baseline, and defined by

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scores 28-30 ('normal', *n*=8,689), 24-27 ('mild dysfunction', *n*=2,231) and <24 ('severe dysfunction', *n*=212). Risks of major cardiovascular events, death and hypoglycaemia and interactions with treatment were assessed using Cox proportional hazards analysis.

Results Relative to normal function, both mild and severe cognitive dysfunction significantly increased the multiple-adjusted risks of major cardiovascular events (HR 1.27, 95% CI 1.11–1.46 and 1.42, 95% CI 1.01–1.99; both $p < 0.05$), cardiovascular death (1.41, 95% CI 1.16–1.71 and 1.56, 95% CI 0.99–2.46; both $p \leq 0.05$) and all-cause death (1.33, 95% CI 1.16–1.54 and 1.50, 95% CI 1.06–2.12; both $p < 0.03$). Severe, but not mild, cognitive dysfunction increased the risk of severe hypoglycaemia (HR 2.10, 95% CI 1.14–3.87; $p = 0.018$). There was no evidence of heterogeneity of treatment effects on cardiovascular outcomes in subgroups defined by cognitive function at baseline.

Conclusions/interpretation Cognitive dysfunction is an independent predictor of clinical outcomes in patients with type 2 diabetes, but does not modify the effects of BP lowering or glucose control on the risks of major cardiovascular events.

Keywords Blood pressure control · Cardiovascular disease risk · Cognitive function · Glucose control · Hypoglycaemia · MMSE · Mortality · Type 2 diabetes

Abbreviations

ADVANCE	Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation
MMSE	Mini Mental State Examination

Introduction

Diabetes and cognitive dysfunction represent serious health problems in the ageing population, with the prevalence of both conditions projected to increase in most parts of the world [1, 2]. A number of studies have reported that cognitive decline is accelerated in patients with diabetes, independently of common cardiovascular risk factors [3–5] and is associated with poor glycaemic control [6]. In a recent meta-analysis, patients with type 2 diabetes were estimated to have a 1.5-fold greater risk of cognitive

dysfunction and 1.6-fold greater risk of dementia compared with people without diabetes [7]. These findings coincide with structural and functional defects demonstrated by various imaging modalities [8], and indicate that cognitive impairment may represent a separate complication alongside retinopathy, nephropathy, neuropathy and cardiovascular disease in patients with type 2 diabetes [8].

Cognitive dysfunction has also been proposed to be a risk factor for cardiovascular disease and mortality in elderly populations [9–11], although this association is probably confounded by the higher prevalence of cardiovascular risk factors such as high BP and type 2 diabetes with increasing age [12]. Among older patients with diabetes, reduced survival has been reported in those with poor cognitive function [13, 14]. However, previous studies have excluded younger patients, which is a drawback since cognitive function deteriorates at a younger age in patients with type 2 diabetes compared with people without diabetes [8].

Few studies have investigated the effects of BP- and glucose-lowering treatments in patients with both type 2 diabetes and cognitive dysfunction. In the absence of clear cardiovascular benefits, such treatments may be used cautiously or even withheld in these patients due to concerns that lower cerebral blood flow or incident hypoglycaemia may exacerbate cognitive decline and even provoke the onset of dementia [8, 15, 16]. The recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, investigated the separate effects of both routine BP lowering and intensive glucose control on vascular outcomes in a broad range of patients with type 2 diabetes [17, 18]. The purpose of the present analyses was to quantify mortality and cardiovascular risks associated with impaired cognitive function in patients with type 2 diabetes, and to compare the effects of the BP-lowering and intensive glucose-control interventions in those with and without cognitive dysfunction.

Methods

ADVANCE was a randomised factorial trial designed to investigate the effects of routine BP lowering and intensive glucose control on vascular outcomes in patients with type 2 diabetes. The main results have been reported previously [17, 18].

Participants A total of 11,140 patients (≥55 years) with a diagnosis of type 2 diabetes (from the age of ≥30 years) and a history of major macro- or microvascular disease or at least one other cardiovascular risk factor, were recruited from 215 centres in 20 countries between June 2001 and

March 2003 [19]. Patients with a definite indication for long-term insulin therapy at baseline or a definite indication for, or contraindication to, one of the study treatments, were excluded from participating in the study. There were no BP or glucose thresholds for study entry.

Randomised treatments Potentially eligible participants entered a 6 week run-in period, during which they received a fixed combination of the ACE inhibitor, perindopril, and thiazide-like diuretic, indapamide. Patients who tolerated and were compliant with the run-in treatment were subsequently randomised, in a factorial design, to continued treatment with perindopril–indapamide or placebo and to intensive glucose control based on the sulfonylurea, gliclazide MR, targeting an HbA_{1c} of ≤6.5%, or to standard glucose control [19]. Median treatment follow-up for the BP-lowering arm of the study was 4.3 years, whereas the glucose-control intervention continued for another 8 months, to be completed after a median follow-up of 5.0 years [17, 18].

Definitions Cognitive function was assessed using the Mini Mental State Examination (MMSE) at baseline, at 2 yearly intervals during follow-up, and at study completion. Cognition was defined as 'normal' for MMSE scores of ≥28, as 'mild dysfunction' for scores of 24–27, and as 'severe dysfunction' for scores <24 [20]. Patients with an MMSE score of <24 or where there was suspicion of dementia, required referral to an appropriately qualified specialist for diagnosis of dementia according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM IV), unless a diagnosis of dementia had been made beforehand. The Modification of Diet in Renal Disease equation was used to calculate the estimated GFR [21].

Outcomes The outcomes for the current analysis were major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death), all-cause death, cardiovascular death, major coronary events (non-fatal myocardial infarction and death caused by coronary disease), major strokes (non-fatal and fatal stroke), dementia, and any hypoglycaemia (defined as the presence of typical symptoms without other apparent cause or a blood glucose <2.8 mmol/l), and classified as severe (when patients had transient central nervous system dysfunction requiring external assistance) or mild (when self-treated) [17, 19].

Statistical analysis The risks of clinical outcomes were analysed by baseline cognitive status using the MMSE categories defined above. Differences in baseline variables between cognitive function subgroups were tested using a Student's *t* test, Mann–Whitney test or χ^2 test, as appropriate. The risks of events associated with baseline cognitive function were estimated using Cox proportional hazards models, with adjustment for potential confounding baseline covariates: age, sex, treatment allocation, educational status, diabetes duration, systolic BP, history of currently treated hypertension, HbA_{1c}, LDL-cholesterol, HDL-cholesterol, BMI, history of macrovascular or microvascular disease, current smoking and current alcohol intake. As the MMSE data were not normally distributed, the risks of clinical outcomes were also examined using baseline MMSE score as a continuous variable in the Cox models.

To determine the extent to which baseline cognitive function modified the effects of randomised treatment, the data were analysed using unadjusted Cox models, according to the principle of intention-to-treat, using 4.3 years of follow-up for the BP-lowering intervention and 5.0 years of follow-up for the glucose-control intervention. Tests of the homogeneity of treatment effects between the cognitive function subgroups were performed by adding an interaction term to the relevant Cox model. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA). Data are reported with 95% CIs and all *p* values were calculated using two-tailed tests.

Results

MMSE scores were obtained at baseline in all but eight patients (<0.1%), who were excluded from the analyses. In the entire study population the median MMSE score at baseline was 29 (interquartile range 28–30): 8,689 patients (78.1%) had an MMSE score of ≥28, 2,231 patients (20.0%) had a score of 24–27, and 212 patients (1.9%) had a score <24, of whom 31 were thought to have dementia. Table 1 shows the baseline characteristics of patients according to level of cognitive function. Patients with a lower MMSE score were older and more often female, and had longer duration of diabetes, fewer years of formal education, and more often diabetic nephropathy or a history of stroke. They also had slightly higher levels of HbA_{1c} and systolic BP, and lower levels of estimated GFR. There were no differences according to assignment to intervention or control groups (data not shown).

Impact of baseline cognitive function on cardiovascular outcomes and mortality During a median follow-up of 5.0 years, a total of 1,147 patients (10.3%) developed a major cardiovascular event. In unadjusted analyses, the risks of these events were 52% and 110% higher in patients with mild and severe cognitive dysfunction, respectively,

Table 1 Baseline characteristics of patients

Characteristics	MMSE score			p value for trend
	28–30 (n=8,689)	24–27 (n=2,231)	≤23 (n=212)	
Age (years)	65 (6.3)	67 (6.4)	68 (6.2)	<0.001
Female, n (%)	3,538 (40.7)	1,078 (48.3)	114 (53.8)	<0.001
Age of completion of highest education, years (SD)	19 (7.2)	16 (6.8)	12 (7.3)	<0.001
Duration of diabetes (years)	7.9 (6.3)	8.0 (6.5)	8.3 (7.0)	0.469
History of major cardiovascular disease, n (%)	2,761 (31.8)	735 (32.9)	91 (42.9)	0.002
Myocardial infarction, n (%)	1,039 (12.0)	264 (11.8)	30 (14.2)	0.607
Stroke, n (%)	714 (8.2)	260 (11.7)	47 (22.2)	<0.001
History of major microvascular disease, n (%)	839 (9.7)	281 (12.6)	35 (16.5)	<0.001
Macroalbuminuria, n (%)	280 (3.2)	107 (4.8)	17 (8.0)	<0.001
Major diabetic eye disease, n (%)	588 (6.8)	185 (8.3)	22 (10.4)	0.009
History of hypertension, n (%)	5,918 (68.1)	1,586 (71.1)	145 (68.4)	0.024
Past smoker, n (%)	3,733 (43.0)	865 (38.8)	75 (35.4)	<0.001
Current smoker, n (%)	1,345 (15.5)	309 (13.9)	27 (12.7)	0.099
Current alcohol use, n (%)	2,777 (32.0)	572 (25.6)	44 (20.8)	<0.001
HbA$_{1c}$, % (SD)	7.5 (1.5)	7.6 (1.7)	7.7 (1.8)	<0.001
Systolic BP, mmHg (SD)	144 (21.2)	147 (22.8)	147 (22.5)	<0.001
Diastolic BP, mmHg (SD)	81 (10.8)	80 (11.3)	80 (10.7)	0.102
Serum total cholesterol, mmol/l (SD)	5.2 (1.2)	5.3 (1.2)	5.2 (1.1)	0.004
Serum creatinine, μmol/l	86.3 (24.6)	87.6 (28.2)	85.7 (23.9)	0.117
Estimated GFR, ml min^{-1} 1.73 m^{-2} (SD)[a]	83.7 (28.6)	77.4 (27.8)	75.3 (28.2)	<0.001
Estimated GFR, <60 ml min^{-1} 1.73 m^{-2}, n (%)[a]	1,682 (19.4)	582 (26.2)	64 (30.3)	<0.001
UACR, mg/mmol (interquartile range)[b]	1.61 (0.79–4.20)	1.93 (0.90–5.10)	1.89 (0.90–7.23)	<0.001
BMI (kg/m^2)	28.4 (5.2)	28.2 (5.0)	28.2 (6.3)	0.104

[a] Estimated GFR was calculated using the Modification of Diet in Renal Disease equation [21]

[b] UACR, urinary albumin to creatinine ratio

compared with those with normal cognitive function (both p<0.0001). These excess risks were attenuated by adjustment for age, sex, treatment allocation, education and a range of cardiovascular risk factors, but remained significant (Table 2). The unadjusted and adjusted risks of major coronary events and of stroke in patients with cognitive dysfunction were elevated to a similar extent to that of the overall risk of major cardiovascular events.

A total of 1,031 patients (9.3%) died during follow-up, about half from cardiovascular causes (n=542, 4.9%). The risks of all-cause and cardiovascular mortality were significantly higher in patients with mild and severe cognitive dysfunction, compared with no dysfunction, in both crude and age-, sex-, treatment allocation- and education-adjusted analyses (all p<0.001, Table 2). After further adjustment, the all-cause mortality risks were still 33% and 50% higher in patients with mild and severe cognitive dysfunction, respectively, compared with patients with normal cognitive function (both p<0.03). The increased risk of death was mainly driven by excess cardiovascular mortality in these patient groups.

Impact of baseline cognitive function on hypoglycaemia The risk of severe hypoglycaemia, but not of any hypoglycaemia, was moderately elevated in patients with mild cognitive dysfunction and markedly elevated in patients with severe cognitive dysfunction compared with those with normal cognitive function (Fig. 1). After adjustment for age, sex, treatment allocation and educational status, the risk of severe hypoglycaemia was no longer elevated in patients with mild cognitive dysfunction. However, in patients with severe cognitive dysfunction, even after adjustment for several covariates, the risk of severe hypoglycaemia remained more than twofold higher than in patients with normal cognitive function (p=0.018).

Analyses using MMSE score as a continuous risk factor In age-, sex-, treatment allocation- and education-adjusted analyses, each unit of lower MMSE score at baseline increased the risk of cardiovascular events by 8% (95% CI 5–11%), the risk of cardiovascular mortality by 11% (95% CI 8–15%) and that of all-cause mortality by 9% (95% CI 6–12%) (all p<0.0001). Similarly, for every one unit lower

Table 2 Results of crude and adjusted analyses of differences in clinical outcomes and adverse events in patients with mild cognitive impairment vs normal cognitive function, and patients with severe cognitive impairment vs normal cognitive function

Outcome	Crude analysis	p value	Adjusted for treatment, age, sex and education	p value	Adjusted for multiple covariates[a]	p value
Mild cognitive dysfunction vs normal cognitive function						
Major cardiovascular events	1.52 (1.33–1.74)	<0.0001	1.37 (1.20–1.57)	<0.0001	1.27 (1.11–1.46)	0.0006
Major strokes	1.48 (1.20–1.81)	0.0002	1.34 (1.08–1.65)	0.0067	1.21 (0.97–1.49)	0.0884
Major coronary events	1.45 (1.22–1.74)	<0.0001	1.31 (1.09–1.57)	0.0037	1.24 (1.03–1.49)	0.0246
All heart failure	1.78 (1.46–2.19)	<0.0001	1.51 (1.22–1.86)	0.0001	1.40 (1.13–1.73)	0.002
All-cause mortality	1.64 (1.43–1.88)	<0.0001	1.40 (1.22–1.61)	<0.0001	1.33 (1.16–1.54)	<0.0001
Cardiovascular death	1.79 (1.49–2.16)	<0.0001	1.53 (1.27–1.85)	<0.0001	1.41 (1.16–1.71)	0.0006
New-onset dementia	4.74 (3.12–7.19)	<0.0001	3.71 (2.43–5.68)	<0.0001	3.59 (2.34–5.50)	<0.0001
Any hypoglycaemia	0.97 (0.91–1.04)	0.461	0.98 (0.91–1.05)	0.6056	0.98 (0.91–1.06)	0.6258
Severe hypoglycaemia	1.39 (1.03–1.89)	<0.0001	1.17 (0.86–1.60)	0.3232	1.11 (0.81–1.53)	0.5102
Severe cognitive dysfunction vs normal cognitive function						
Major cardiovascular events	2.10 (1.52–2.89)	<0.0001	1.80 (1.30–2.50)	0.0004	1.42 (1.01–1.99)	0.0426
Major strokes	2.01 (1.22–3.32)	0.0063	1.71 (1.03–2.85)	0.0398	1.32 (0.78–2.25)	0.306
Major coronary events	1.97 (1.27–3.05)	0.0303	1.70 (1.09–2.64)	0.0200	1.33 (0.84–2.11)	0.2216
All heart failure	2.33 (1.41–3.85)	0.0010	1.80 (1.08–3.01)	0.0241	1.52 (0.91–2.55)	0.1108
All-cause mortality	2.25 (1.62–3.13)	<0.0001	1.83 (1.31–2.56)	0.0004	1.50 (1.06–2.12)	0.0225
Cardiovascular death	2.76 (1.81–4.21)	<0.0001	2.21 (1.43–3.40)	0.0003	1.56 (0.99–2.46)	0.0552
New-onset dementia	23.4 (13.7–40.0)	<0.0001	16.6 (9.37–29.6)	<0.0001	16.0 (8.93–28.8)	<0.0001
Any hypoglycaemia	1.04 (0.85–1.27)	0.696	1.05 (0.86–1.29)	0.6158	1.03 (0.84–1.26)	0.8059
Severe hypoglycaemia	3.86 (2.24–6.67)	<0.0001	2.86 (1.63–5.05)	0.0003	2.10 (1.14–3.87)	0.018

Values are HRs (95% CIs)

Normal cognitive function, MMSE score ≥28; mild cognitive impairment, MMSE score 24–27; severe cognitive impairment, MMSE score ≤23

[a] Adjusted for treatment allocation, age, sex, education, diabetes duration, history of cardiovascular disease, history of microvascular disease, history of hypertension, BMI, systolic BP, HDL-cholesterol, LDL-cholesterol, smoking, alcohol use and HbA_{1c}

MMSE score, the risk of severe hypoglycaemia was increased by 10% (95% CI 4–16%; $p=0.0010$). In the multiple-adjusted model, one unit lower MMSE score remained associated with increased risks of cardiovascular events (6%, 95% CI 3–9%; $p<0.0001$), cardiovascular mortality (9%, 95% CI 5–13%; $p<0.0001$), all-cause mortality (8%, 95% CI 5–11%; $p<0.0001$) and severe hypoglycaemia (7%, 95% CI 1–13%; $p=0.0303$).
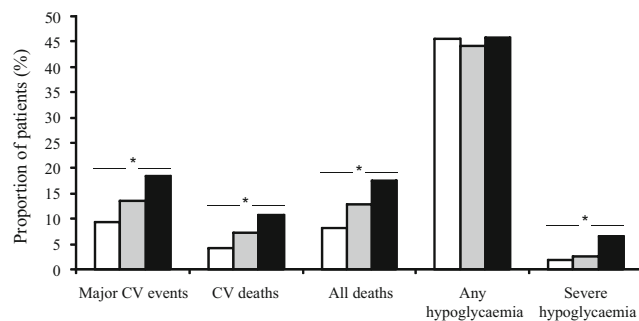

Fig. 1 Proportion of patients with clinical outcomes during follow-up according to cognitive function status at baseline. White bars, normal cognitive function; grey bars, mild cognitive dysfunction; black bars, severe cognitive dysfunction. CV, cardiovascular. *p for trend <0.0001
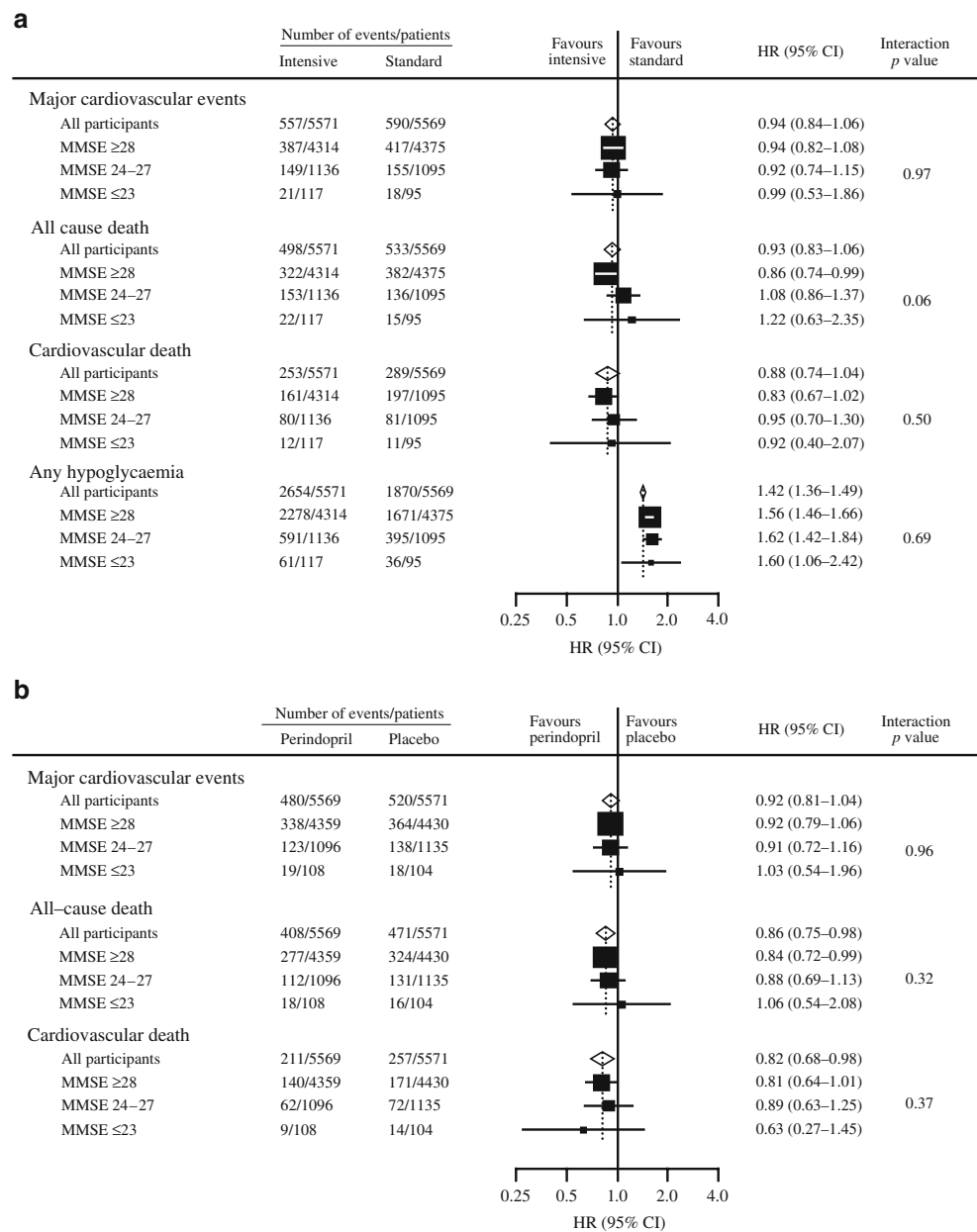
Effects of randomised BP-lowering and glucose-control treatments in cognitive function subgroups There was no indication that baseline cognitive function modulated the effects on major cardiovascular events or cardiovascular death of either the BP-lowering or the intensive glucose-control intervention evaluated in ADVANCE (all p values for interaction ≥0.3), but there was a suggestion of heterogeneity with respect to the effect of glucose control on all-cause mortality (p for interaction=0.06) (Fig. 2). Neither intervention modified the risk of cognitive decline or dementia in any of the subgroups (data not shown). As anticipated, intensive glucose control increased the risk of any hypoglycaemia (Fig. 2) but did so to a similar relative extent in the three cognitive function subgroups (p for interaction=0.69).

Discussion

In these analyses of the ADVANCE study, patients with type 2 diabetes and mildly impaired cognitive function, as assessed by the MMSE were at increased risk of cardio-

Fig. 2 Effects of randomised interventions on major clinical outcomes. The centres of the diamonds represent the estimates and their widths, with the 95% CIs for overall treatment effect. Solid boxes represent estimates of treatment effect in subgroups: the centres of the boxes are placed at the estimates of effect, the areas of boxes are proportional to the number of events, and horizontal lines represent the corresponding 95% CIs. The vertical dotted line represents the point estimate for overall effect. The interaction *p* value tested the consistency of treatment effect in subgroups. **a** Effect of intensive vs standard glucose control on major cardiovascular events, all-cause mortality, cardiovascular death and hypoglycaemia in subgroups of participants defined by cognitive function at baseline. **b** Effect of routine perindopril–indapamide vs placebo BP-lowering treatment on major cardiovascular events, all-cause mortality and cardiovascular death in subgroups of participants defined by cognitive function at baseline

a

	Number of events/patients				HR (95% CI)	Interaction *p* value
	Intensive	Standard				
Major cardiovascular events						
All participants	557/5571	590/5569			0.94 (0.84–1.06)	
MMSE ≥28	387/4314	417/4375			0.94 (0.82–1.08)	
MMSE 24–27	149/1136	155/1095			0.92 (0.74–1.15)	0.97
MMSE ≤23	21/117	18/95			0.99 (0.53–1.86)	
All cause death						
All participants	498/5571	533/5569			0.93 (0.83–1.06)	
MMSE ≥28	322/4314	382/4375			0.86 (0.74–0.99)	
MMSE 24–27	153/1136	136/1095			1.08 (0.86–1.37)	0.06
MMSE ≤23	22/117	15/95			1.22 (0.63–2.35)	
Cardiovascular death						
All participants	253/5571	289/5569			0.88 (0.74–1.04)	
MMSE ≥28	161/4314	197/1095			0.83 (0.67–1.02)	
MMSE 24–27	80/1136	81/1095			0.95 (0.70–1.30)	0.50
MMSE ≤23	12/117	11/95			0.92 (0.40–2.07)	
Any hypoglycaemia						
All participants	2654/5571	1870/5569			1.42 (1.36–1.49)	
MMSE ≥28	2278/4314	1671/4375			1.56 (1.46–1.66)	
MMSE 24–27	591/1136	395/1095			1.62 (1.42–1.84)	0.69
MMSE ≤23	61/117	36/95			1.60 (1.06–2.42)	

Favours intensive — Favours standard
0.25 0.5 1.0 2.0 4.0
HR (95% CI)

b

	Number of events/patients				HR (95% CI)	Interaction *p* value
	Perindopril	Placebo				
Major cardiovascular events						
All participants	480/5569	520/5571			0.92 (0.81–1.04)	
MMSE ≥28	338/4359	364/4430			0.92 (0.79–1.06)	
MMSE 24–27	123/1096	138/1135			0.91 (0.72–1.16)	0.96
MMSE ≤23	19/108	18/104			1.03 (0.54–1.96)	
All–cause death						
All participants	408/5569	471/5571			0.86 (0.75–0.98)	
MMSE ≥28	277/4359	324/4430			0.84 (0.72–0.99)	
MMSE 24–27	112/1096	131/1135			0.88 (0.69–1.13)	0.32
MMSE ≤23	18/108	16/104			1.06 (0.54–2.08)	
Cardiovascular death						
All participants	211/5569	257/5571			0.82 (0.68–0.98)	
MMSE ≥28	140/4359	171/4430			0.81 (0.64–1.01)	
MMSE 24–27	62/1096	72/1135			0.89 (0.63–1.25)	0.37
MMSE ≤23	9/108	14/104			0.63 (0.27–1.45)	

Favours perindopril — Favours placebo
0.25 0.5 1.0 2.0 4.0
HR (95% CI)

vascular events and death. Patients with more severe cognitive dysfunction were at even greater risk of such events and were also at increased risk of severe hypoglycaemia. For all these outcomes, there was an inverse and continuous correlation with the MMSE score, in that the lower the MMSE score the higher the event risk. There was no evidence to suggest that cognitive dysfunction modified the response to BP-lowering or glucose-control treatments in the management of cardiovascular risk. Thus, patients with cognitive dysfunction appeared to benefit to the same extent as patients with normal cognitive function from interventions that reduce the risks of cardiovascular outcomes. As previously reported, in this group of patients with type 2 diabetes neither BP lowering nor intensive glucose control had any effect on the development of cognitive impairment and dementia [17, 18].

Our findings of increased mortality and cardiovascular disease risks associated with baseline cognitive impairment are in agreement with observations in the general elderly population [10, 11, 13, 22], and in older patients with diabetes [14]. Adjusting for level of education did not materially alter these risks (data not shown, but available on request), making it unlikely that our results were merely an extension of a low level of intelligence, which by itself carries an increased cardiovascular risk [23, 24]. Much of the increased risk may be explained by the higher prevalence of cardiovascular risk factors among patients with cognitive dysfunction. However, although attenuated,

the association between impaired cognitive function and major clinical outcomes in our study remained statistically significant even after controlling for these risk factors. This may be caused in part by incomplete adjustment for and consequent overestimation of covariates measured with substantial error, and in part to covariates that were unmeasured or otherwise unknown, such as subclinical vascular disease or poor compliance with pharmacological and non-pharmacological treatments [25].

A potential biological factor that could explain the link between cognitive dysfunction and cardiovascular events concerns chronic hyperinsulinaemia or insulin resistance. Chronic hyperinsulinaemia has been associated with both cognitive dysfunction [26] and increased risk of cardiovascular death [27]. There has also been an association between low beta cell function, a determinant of type 2 diabetes and thus of chronic hyperinsulinaemia later in life, and Alzheimer's disease [28]. Insulin resistance, a well-known risk factor for atherosclerosis [29], has been associated with vascular dementia [28]. Although once considered insulin-insensitive, the brain is now thought to depend on intact insulin signalling for several aspects of its function, including memory formation. Chronic hyper-insulinaemia and peripheral insulin resistance may impair insulin signalling by reducing cerebral insulin uptake [30] and insulin action [31], respectively. They may also impair memory function and precede Alzheimer's disease by increasing the levels of inflammatory factors and β-amyloid in the brain [32].

Patients with severe cognitive dysfunction were at twofold higher risk of severe hypoglycaemia than patients with normal cognitive function. Thus while both patients and physicians share concern that severe hypoglycaemia may be implicated in the aetiology of cognitive impairment [8], they should also be aware of a possible causal relationship in the opposite direction. The higher risk of severe hypoglycaemia was independent of recognised risk factors such as old age, low HbA$_{1c}$, long duration of diabetes and cardiovascular risk factors. However, it is conceivable that incomplete adherence to or inappropriate use of the glucose-control regimen, which could not be assessed with certainty, might have played a role. Management of diabetes is complex and heavily dependent on active involvement of patients with respect to drug compliance, glucose testing, meal planning and insulin dose titration. This is a demanding process that could cause greater difficulties for patients with severe cognitive impairment. Nevertheless, our analyses did not reveal increased relative risks of hypoglycaemia associated with intensive glucose-control intervention in patients with mild or severe cognitive dysfunction. However, information on mild hypoglycaemia was only collected on the basis of self-reporting, which may be less reliable in the cognitively impaired. Furthermore, there were too few severe hypoglycaemic episodes overall to have adequate power for this subgroup analysis.

There are limited data on the efficacy of risk-factor management in people with impaired cognitive function. Among elderly people with hypertension, BP-lowering treatment was recently reported to reduce the risk of stroke to the same extent as in patients with mildly impaired or normal cognitive function [12]. Our data support these findings in that the relative benefits of BP-lowering treatment and risks of intensive glucose control in patients with type 2 diabetes were largely independent of the level of cognitive function. The greater baseline risk of different outcomes in patients with cognitive dysfunction may translate these similar relative treatments effects into both greater absolute benefits and greater absolute risks (for example severe hypoglycaemia). In this respect, there was some suggestion that cognitive function modified the effect of glucose lowering on survival, in that patients with lower MMSE scores benefited less than those with higher scores. Although this finding was probably caused by chance, it supports the importance of balancing potential benefits and risks for each patient when making treatment decisions. In any case, there seems little justification in denying patients risk-modifying treatment solely on the basis of cognitive impairment.

Some limitations of this study merit consideration. First, the MMSE was originally designed as a screening test for dementia and not especially for the assessment of milder degrees of cognitive dysfunction [33]. However, this limitation may be less relevant for the use of MMSE in cohort or epidemiological studies. Second, at baseline most patients had maximal MMSE scores (i.e. normal cognitive function) with only a small proportion (<2%) demonstrating severe impairment of cognitive function. Thus there was limited statistical power to analyse risks associated with severe cognitive dysfunction. Yet when analysing risks of clinical outcomes by using MMSE as a continuous variable, similar results were yielded, substantiating the validity of our results, at least with respect to mild cognitive dysfunction. As indicated previously, there was insufficient power to analyse the risk of severe hypoglycaemia by randomised glucose-control assignment in cognitive function subgroups.

In conclusion, our data show that cognitive dysfunction further increases the already greater risk of cardiovascular events and death, but does not adversely modify the response to BP- or glucose-lowering treatment in patients with type 2 diabetes. This is clinically relevant, as cognitive decline is common among patients with type 2 diabetes and may influence management [8]. Our data do not support commonly held views [8, 15, 16] suggesting general restraints with regard to cardiovascular risk management

in patients with cognitive impairment. Therefore, rather than denying patients with type 2 diabetes risk-modifying treatment on the basis of cognitive dysfunction, such patients deserve a similar careful balancing of all potential risks and benefits associated with treatment to that of patients with intact cognitive function. Future guidelines may need to address this growing patient group in their directives for clinical care.

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