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Cognitive impairment and risk of cardiovascular events and mortality

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Background Cognitive impairment may increase the risk of all cardiovascular (CV) events. We prospectively evaluated the independent association between Mini-Mental State Examination (MMSE) score and myocardial infarction, stroke, hospital admission for heart failure and mortality, and their CV composite (major CV events), in a large high-risk CV population.

Methods and results Mini-Mental State Examination was recorded at baseline in 30 959 individuals enrolled into two large parallel trials of patients with prior cardiovascular disease or high-risk diabetes and followed for a median of 56 months. We used a Cox regression model to determine the association between MMSE score and incident CV events and non-CV mortality, adjusted for age, sex, education, history of vascular events, dietary factors, blood pressure, smoking, glucose, low-density lipoprotein, high-density lipoprotein, CV medications, exercise, alcohol intake pattern, depression, and psychosocial stress. Patients were categorized into four groups based on baseline MMSE; 30 (reference), 29–27, 26–24, and <24. Compared with patients with an MMSE of 30 ($n = 9624$), those with scores of 29–27 [$n = 13\,867$; hazard ratio (HR) 1.08; 95% confidence intervals (CI) 1.01–1.16], 26–24 ($n = 4764$; HR: 1.15; 95% CI: 1.05–1.26) and <24 ($n = 2704$; HR: 1.35; 95% CI: 1.21–1.50) had a graded increase in the risk of major vascular events ($P < 0.0001$). Mini-Mental State Examination score was significantly associated with each of the individual components of the composite, except myocardial infarction. There was also no association between baseline MMSE and hospitalization for unstable or new angina. Within MMSE domains, impairments in orientation to place (HR: 1.52; 1.25–1.85), attention-calculation (HR: 1.10; 1.02–1.18), recall (HR: 1.10; 1.04–1.16), and design copy (HR: 1.15; 1.06–1.24) were the most predictive of major vascular events and mortality. The magnitude of increased risk of CV events associated with an MMSE <24 was similar to a previous history of stroke.

Conclusion In people at increased CV risk, impairments on baseline cognitive testing are associated with a graded increase in the risk of stroke, congestive heart failure, and CV death, but not coronary events. An MMSE score of <24 increased CV disease risk to the same extent as a previous stroke.

Keywords Cognition • Risk factor • Cardiovascular • Mortality

Introduction

Cardiovascular disease (CVD) is an important risk factor for cognitive impairment and dementia.[1] It is also proposed that cognitive impairment may increase the risk of future CV events. However, the results of previous studies evaluating the association between cognitive function and cardiovascular risk have been inconsistent.[2–12] Moreover, only one of these previous studies evaluated the relationship across the full spectrum of individual CV events, to include stroke, acute coronary syndrome, and congestive heart failure.[12]

An association between cognitive impairment and major CV events would be expected for several reasons. First, risk factors for CV disease (e.g. hypertension, diabetes mellitus, and smoking) are also risk factors for vascular dementia as well as Alzheimer's disease,[13] the most common causes of cognitive decline. Therefore, cognitive impairment may simply be a marker of

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end-organ damage due to covert stroke, thereby identifying a 'high-risk' population. Secondly, patients with cognitive impairment have lifestyle factors that may influence the risk of CV disease, such as reduced fruit and vegetable intake, sedentary activity, and pattern of alcohol intake.[14–16] Thirdly, depression and psychosocial stress, which are more common in patients with cognitive impairment, are risk factors for CV events.[17–19] A potential confounding influence of these factors has been inadequately explored for individual CV events in previous studies.

In this study, we determined the association between cognitive impairment in those without clinical dementia using scores on the Mini-Mental State Examination (MMSE)[20] and risk of CV events (death, stroke, acute coronary syndrome, and hospitalization for heart failure) and death in a cohort of patients with a prior CV event or diabetes mellitus, and explored whether the association could be explained by other factors.

Methods

Population

All participants in the ONTARGET and TRANSCEND trials who completed the MMSE at baseline were included.[21,22] Patients at a high risk of CV disease (aged ≥55 years plus a history of either established CV disease or diabetes mellitus with evidence of end-organ damage) were included. Patients were ineligible if they had symptomatic congestive heart failure, significant valvular disease, or uncontrolled hypertension. The ONTARGET trial was a randomized controlled, double-blind, double-dummy trial comparing the effects of the combination of telmisartan 80 mg daily with ramipril 10 mg daily, ramipril 10 mg daily, or telmisartan 80 mg daily in 25 620 patients. The TRANSCEND trial was a randomized controlled, double-blind trial comparing telmisartan 80 mg daily with placebo in 5926 participants who were intolerant to angiotensin-converting enzyme (ACE) inhibitors. Both trials were conducted in the same time period, used the same eligibility criteria (other than intolerance to ACE-inhibitors) and used the same methods of measurement of baseline risk factors and outcome events. Other antihypertensive medication was allowed. After randomization, patients were followed at 6 weeks, 6 months and then every 6 months thereafter for a median of 56 months. At each follow-up visit, episodes of myocardial infarction, stroke or congestive cardiac failure, or other events were recorded. Participants were recruited from 733 collaborating centres in 40 countries between November 2001 and May 2004. Approval was obtained from the institutional ethics committee of each centre, and all participants provided written informed consent. Primary results of both trials have been published previously.[21,22]

Outcome measures

The primary composite outcome for both trials was CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure. All primary study outcomes were adjudicated centrally using standard diagnostic criteria and available supporting information. For the current analyses, we also included non-CV death and hospital admission for unstable angina.

Cognitive testing

Cognitive function was assessed in all patients at baseline, at 2-year follow-up and during the penultimate visit (i.e. that immediately before the final visit), using the MMSE. For the primary analysis, we used baseline MMSE assessment only. The MMSE includes 10 domain items, which measure orientation to time (5 points), orientation to place (5 points), registration (3 points), attention and calculation (5 points), recall (3 points), naming and repetition (3 points), comprehension (3 points), reading ability (1 point), writing ability (1 point), and design copy (1 point), the latter being a brief measure of visual construction. The MMSE scale ranges from 0 to 30, with a higher score indicating better cognitive performance. For each successfully completed item on the MMSE, a score of 1 point (to a maximum of 30) is awarded. In situations where the participant did not answer all questions, the weighted score of the completed answers was used. Of participants who completed the MMSE at baseline, 97.7% completed all 30 questions, and 99.6% completed at least 27 questions. For the current study, the baseline MMSE scores were categorized as 30 (reference), 29–27, 26–24, and <24. MMSE scores of <26 and <24 has been used as a conventional cut-point for cognitive impairment.[23,24] Contextually appropriate translations of the MMSE were used in several countries (Austria, Belgium, Czech Republic, Germany, Greece, Netherlands, Finland, Norway, Sweden, S. Africa, and S. Korea), but most investigators administered a standard English language version to participants in the local language, if necessary. Investigators and coordinators underwent training sessions before to commencement, and monitoring visits were undertaken during the course of the study to ensure uniform adherence to procedures.

Education, alcohol, diet, exercise, depression, and psychosocial stress

All variables were collected at the time of randomization; other than changes in blood pressure, which were collected during the follow-up. Education was categorized as: none, 1–8 years, 9–12 years, trade school/technical college, and college/university. Participants were considered 'English speaking' if they were recruited from a site in an English-speaking country. Creatinine clearance was estimated from the serum creatinine using the Cockcroft–Gault formula.[25] Smoking was categorized as never (reference), former, or current. Pattern of alcohol intake was defined as never/former, current (moderate), and current (binge). Binge alcohol consumption was defined as consumption of more than five drinks in a single day at least once per month. Fruit and vegetable intake were measured with a semi-quantitative food frequency questionnaire, based on the participant's impression of average consumption per month, week, or day using a questionnaire used in the INTERHEART study.[26] The exercise level was categorized as mainly sedentary (reference), exercise two to four times per week, five to six times per week, and daily exercise, and consistent with measures used in the INTERHEART study.[26] Depression was based on a reported history of 'feeling sad, low in spirits or depressed for 2 weeks or more' in the previous year. Severity of depression was based on the number of other depressive symptoms (0–7) and whether the participant had received antidepressant therapy and categorized into: none (reference), mild (0–2 symptom), moderate (3–4 symptoms), and severe (≥4 symptoms or received treatment). Psychosocial stress was based on a composite of patient-reported stress at work, stress at home (never, some periods, several periods, or permanent), and financial stress (little, none, moderate, or severe) over the previous year. A composite score was derived from these domains and categorized into none/mild, moderate, and severe psychosocial stress. The questions included for depression and psychosocial stress were based on INTERHEART study questionnaire.[17]

Statistical analysis

Baseline differences in characteristics between participants in different MMSE score categories were compared using the χ^2 test and ANOVA

test, as shown in *Table 1*. We estimated the risk of CV events associated with the MMSE score (categorized overall score and dichotomized individual domains) using the Cox proportional hazards model. We generated models for each of the following outcomes and a composite of the CV outcomes (excluding unstable angina): CV mortality, non-CV mortality, myocardial infarction (fatal and non-fatal), stroke (fatal and non-fatal), and hospitalization for congestive heart failure and unstable angina. To explore the influence of potential confounders, we added variables into the regression model in the following groupings: (i) age, sex, education, English-speaking,[27] region, prior history of stroke or myocardial infarction and creatinine clearance, co-morbid vascular risk factors (hypertension, baseline blood pressure and change in blood pressure from baseline to final follow-up, LDL, HDL, BMI, diabetes mellitus and baseline glucose, atrial fibrillation, and smoking), treatment with statins, ACE-inhibitors, calcium antagonists, β-blockers, anticoagulants, and antiplatelet therapy and; (ii) lifestyle and psychosocial factors including: fruit and vegetable consumption, level of exercise, pattern of alcohol intake, depression, and psychosocial stress. For the primary analysis, the MMSE score was categorized as 30 (reference), 29–27, 26–24, and <24. The standard cut-off MMSE score of <24 was used as a conventional cut-point for 'possible' dementia. We tested for interactions between baseline MMSE score, and each of the following variables: age, previous history of hypertension and baseline blood pressure, formal education level, previous history of stroke, alcohol intake pattern, depression, psychosocial stress, fruit and vegetable intake, and level of physical activity. In a secondary analysis, we generated a multivariable model that included individual domains within the MMSE, orientation (time and place), registration, attention-calculation, recall, naming-repetition, comprehension, reading, writing, and design copy. Kaplan–Meier curves were generated for CV death, myocardial infarction, stroke, hospitalization for heart failure, adjusted for all covariates. We also evaluated the association between decline in MMSE score (from baseline to first follow-up MMSE, either 2-year follow-up or penultimate visit) and subsequent risk of CV event from time of follow-up MMSE to final follow-up in a multivariable model that included all variables in the primary model and baseline MMSE score. Data are reported with hazard ratios (HR) and 95% confidence intervals (CI). All analyses were conducted using SAS Version 8.2 for Unix (SAS Institute, Inc., Cary, NC, USA).

Results

In total, 31 546 were enrolled into the ONTARGET and TRANSCEND trials. Of these, 30 959 participants (98.1%) completed a baseline MMSE and are included in the current analyses. Loss to follow-up was 0.2%. Participants with reduced MMSE scores were older, had fewer years of formal education, had lower intake of fruit and vegetables, were less likely to be current smokers or consume alcohol and more likely to be female, have a previous history of stroke, hypertension, diabetes mellitus, atrial fibrillation, and a sedentary lifestyle (*Table 1*).

Mini-Mental State Examination and risk of cardiovascular events and mortality

Cardiovascular and non-cardiovascular mortality

On follow-up, 12% of participants died, ranging from 9.3% in the group with baseline MMSE of 30–21.3% in the group with an MMSE of 24 or less ($P < 0.0001$) (*Table 2*). Sixty per cent of deaths were attributed to a CV cause (*Table 2*). Compared with an MMSE of 30, participants with a MMSE scores of 29–27 (HR: 1.08; 95% CI: 1.00–1.18), 26–24 (HR: 1.28; 95% CI: 1.15–1.42), and <24 (HR: 1.68; 95% CI: 1.49–1.90) were associated with a graded increase in risk of all-cause mortality on multivariable analyses. Baseline MMSE score was a significant predictor of both CV and non-CV mortality (*Figure 2*). Within the common causes of non-CV death, there was a significant association between MMSE and infectious and respiratory causes of death, but no association with cancer, injury, gastrointestinal, or neurological causes other than stroke (*Table 2*).

Stroke

On follow-up, 1374 (4.4%) of participants experienced a stroke, ranging from 3.3% in the group with baseline MMSE of 30 to 7.0% in the group with an MMSE of 24 or less ($P < 0.0001$). Compared with an MMSE of 30, participants with a MMSE scores of 29–27 (HR: 1.19; 95% CI: 1.04–1.37), 26–24 (HR: 1.30; 95% CI: 1.09–1.55), and <24 (HR: 1.44; 95% CI: 1.17–1.77) were associated with a graded increase in risk of stroke on multivariable analyses. (*Figure 2* and *Table 3*).

Myocardial infarction, hospitalization for unstable or new angina

On follow-up, 1527 (4.9%) of participants experienced a myocardial infarction, ranging from 4.7% in the group with baseline MMSE of 30 to 5.0% in the group with an MMSE of 24 or less ($P = 0.06$). We did not find an association between MMSE score and risk of myocardial infarction [MMSE 26–24 (HR: 1.11; 95% CI: 0.94–1.30) and MMSE <24 (HR: 0.99; 95% CI: 0.79–1.22)] (*Figure 2*) or for admission for unstable angina or new angina [MMSE 26–24 (HR: 1.11; 95% CI: 0.95–1.29) and MMSE <24 (HR: 1.12; 95% CI: 0.91–1.37)].

Congestive heart failure

On follow-up, 1314 (4.2%) of participants were hospitalized for congestive heart failure, ranging from 3.2% in the group with baseline MMSE of 30 to 6.8% in the group with an MMSE of 24 or less ($P < 0.0001$). Compared with an MMSE of 30, participants with a MMSE scores of 29–27 (HR: 1.16; 95% CI: 1.00–1.34), 26–24 (HR: 1.24; 95% CI: 1.04–1.49), and <24 (HR: 1.38; 95% CI: 1.12–1.71) were associated with a graded increase in risk of hospitalization for congestive heart failure on multivariable analyses (*Figure 2* and *Table 3*).

Prior stroke or myocardial infarction

On multivariable analyses, a previous history of stroke and myocardial infarction was associated with an HR of 1.40 (95% CI: 1.31–1.50) and 1.43 (95% CI: 1.34–1.53), respectively, for the composite of all CV outcomes.

Subgroup analyses and interaction between Mini-Mental State Examination and confounders

The increased risk of CV events associated with reduced baseline MMSE score was similar in those younger or older than 75 years, participants from English- and non-English-speaking regions, men and women, different levels of formal education, and those with and without a previous history of stroke and hypertension (*Figure 3*). Among patients with diabetes mellitus without a

Table 1 Baseline patient characteristics by Mini-Mental State Examination categories

	Baseline MMSE Score					
	All	**30**	**29–27**	**26–24**	**<24**	***P*-value**
n	30 959	9624	13 867	4764	2704	
Age (mean; SD)	66.5 (7.2)	65.1 (6.9)	66.6 (7.2)	67.8 (7.2)	68.6 (7.6)	<0.0001
Female, *n* (%)	9174 (29.6)	2471 (25.7)	3799 (27.4)	1650 (34.6)	1254 (46.4)	<0.0001
English, *n* (%)	10 259 (33.1)	3020 (31.4)	5027 (36.3)	1513 (31.8)	699 (25.9)	<0.0001
Educational level						
None	1120 (3.6)	102 (1.1)	251 (1.8)	220 (4.6)	547 (20.2)	<0.0001
1–8 years	9310 (30.1)	1892 (19.7)	3963 (28.6)	2032 (42.7)	1423 (52.6)	
9–12 years	9125 (29.5)	2897 (30.1)	4412 (31.8)	1350 (28.3)	466 (17.2)	
Trade/Technical	5518 (17.8)	2049 (21.3)	2634 (19.0)	670 (14.1)	165 (6.1)	
College/University	5884 (19.0)	2682 (27.9)	2607 (18.8)	492 (10.3)	103 (3.8)	
PH MI, *n* (%)	14 992 (48.4)	4845 (50.3)	6833 (49.3)	2186 (45.9)	1128 (41.7)	<0.0001
PH stroke/TIA, *n* (%)	6520 (21.1)	1728 (18.0)	2816 (20.3)	1119 (23.5)	857 (31.7)	<0.0001
Hypertension, *n* (%)	21 762 (70.3)	6481 (67.3)	9642 (69.5)	3515 (73.8)	2124 (78.6)	<0.0001
Baseline systolic BP (SD)	141.6 (17.3)	141.4 (16.8)	141.6 (17.5)	142.2 (17.5)	143.0 (17.5)	<0.0001
Change in systolic BP (SD)	−5.5 (21.8)	−6.1 (21.0)	−5.7 (21.6)	−4.7 (22.9)	−4.4 (23.5)	0.0001
Diabetes mellitus, *n* (%)	11 547 (37.3)	3308 (34.4)	5081 (36.6)	1928 (40.5)	1230 (45.5)	<0.0001
Glucose (mean; SD)	6.7 (2.5)	6.6 (2.4)	6.6 (2.5)	6.8 (2.6)	7.0 (3.1)	<0.0001
Atrial fibrillation, *n* (%)	1016 (3.3)	258 (2.7)	438 (3.2)	191 (4.0)	129 (4.8)	<0.0001
LDL (mean; SD)	2.94 (1.0)	2.95 (1.0)	2.90 (1.0)	3.0 (1.0)	3.10 (1.0)	<0.0001
HDL (mean; SD)	1.26 (0.4)	1.27 (0.4)	1.26 (0.4)	1.27 (0.4)	1.26 (0.4)	0.4
BMI (mean; SD)	28.1 (4.5)	28.2 (4.5)	28.1 (4.5)	28.1 (4.6)	27.9 (4.9)	0.14
Creatinine clear (mean; SD)	93.9 (24.6)	92.8 (22.5)	94.3 (24.7)	94.7 (25.8)	94.8 (28.2)	<0.0001
Fruit + veg intake/day (SD)	3.7 (3.0)	3.8 (2.9)	3.8 (3.2)	3.6 (2.9)	3.4 (2.6)	<0.0001
Smoking status, *n* (%)						
Never	11 611 (37.5)	3500 (36.4)	4775 (34.4)	1970 (41.4)	1366 (50.5)	<0.0001
Current	3719 (12.0)	1277 (13.3)	1673 (12.1)	509 (10.7)	260 (9.6)	
Former	15 596 (50.4)	4835 (50.2)	7407 (53.4)	2278 (47.8)	1076 (39.8)	
Alcohol intake, *n* (%)						
Never/former	18 955 (61.2)	5517 (57.3)	8071 (58.2)	3212 (67.4)	2155 (79.7)	<0.0001
Current (moderate)	11 415 (36.9)	3909 (40.6)	5516 (39.8)	1469 (30.8)	521 (19.3)	
Current (Binge)	587 (1.9)	197 (2.0)	280 (2.0)	82 (1.7)	28 (1.0)	
Exercise, *n* (%)						
Mainly sedentary	7121 (23.0)	1755 (18.2)	2929 (21.1)	1287 (27.0)	1150 (42.5)	<0.0001
<1/week	3492 (11.3)	1233 (12.8)	1413 (10.2)	544 (11.4)	302 (11.2)	
2–4/week	7059 (22.8)	2462 (25.6)	3210 (23.1)	982 (20.6)	405 (15.0)	
5–6/week	2384 (7.7)	761 (7.9)	1155 (8.3)	308 (6.5)	160 (5.9)	
Everyday	10 898 (35.2)	3412 (35.5)	5158 (37.2)	1642 (34.5)	686 (25.4)	
ACE-inhibitor, *n* (%)	17 919 (57.9)	5317 (55.2)	8039 (58.0)	2869 (60.2)	1694 (62.6)	<0.0001
β-Blockers, *n* (%)	17 694 (57.2)	5665 (58.9)	7984 (57.6)	2678 (56.2)	1367 (50.6)	<0.0001
Calcium antagonists, *n* (%)	10 663 (34.4)	3198 (33.2)	4805 (34.7)	1678 (35.2)	982 (36.3)	<0.007
Diuretics, *n* (%)	8939 (28.9)	2485 (25.8)	3893 (28.1)	1510 (31.7)	1051 (38.9)	<0.001
Antiplatelet, *n* (%)	24 967 (80.6)	7873 (81.8)	11 288 (81.4)	3743 (78.6)	2063 (76.3)	<0.001
Anticoagulant, *n* (%)	2304 (7.4)	649 (6.7)	1056 (7.6)	387 (8.1)	212 (7.8)	0.01
Statin, *n* (%)	18 727 (60.5)	5929 (61.6)	8703 (62.8)	2724 (57.2)	1371 (50.7)	<0.0001

SD, standard deviation; MI, myocardial infarction; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; PH, past history.
*P-value: χ^2 for categorical variables and ANOVA test for continuous variables

Table 2 Causes of death on follow-up by Mini-Mental State Examination categories

	Baseline MMSE					
	All	**30**	**29–27**	**26–24**	**<24**	***P*-trend***
	30 959	**9624**	**13 867**	**4764**	**2704**	
All deaths	3701 (12.0)	891 (9.3)	1554 (11.2)	680 (14.3)	576 (21.3)	<0.0001
CV death	2221 (7.2)	542 (5.6)	917 (6.6)	382 (8.0)	380 (14.1)	<0.0001
MI	198 (0.6)	50 (0.5)	81 (0.6)	43 (0.9)	24 (0.9)	0.07
Stroke	176 (0.6)	34 (0.4)	72 (0.5)	33 (0.7)	37 (1.4)	0.004
CHF	245 (0.8)	65 (0.7)	96 (0.7)	38 (0.8)	46 (1.7)	0.5
Documented arrhythmia	44 (0.1)	11 (0.1)	26 (0.2)	7 (0.1)	0 (0.0)	0.18
Presumed CV Death	565 (1.8)	117 (1.2)	230 (1.7)	95 (2.0)	123 (4.5)	<0.0001
Unexpected Death	786 (2.5)	216 (2.2)	319 (2.3)	132 (2.8)	119 (4.4)	0.006
Other CV Causes	207 (0.7)	49 (0.5)	93 (0.7)	34 (0.7)	31 (1.1)	0.09
Non-CV Death	1480 (4.8)	349 (3.6)	637 (4.6)	298 (6.3)	196 (7.2)	<0.0001
Cancer	778 (2.5)	200 (2.1)	370 (2.7)	148 (3.1)	60 (2.2)	0.2
Infection	215 (0.7)	43 (0.4)	72 (0.5)	55 (1.2)	45 (1.7)	0.0002
Respiratory	108 (0.3)	25 (0.3)	39 (0.3)	23 (0.5)	21 (0.8)	0.045
Gastrointestinal	59 (0.2)	13 (0.1)	23 (0.2)	14 (0.3)	9 (0.3)	0.5
Neurological (non-stroke)	28 (0.1)	8 (0.1)	9 (0.1)	6 (0.1)	5 (0.2)	0.3
Injury	45 (0.1)	10 (0.1)	21 (0.2)	10 (0.2)	4 (0.1)	0.2
Other non-CV death	315 (1.0)	68 (0.7)	125 (0.9)	59 (1.2)	63 (2.3)	0.0001

CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure.
*Adjusted *P*-value for all covariates in multivariable model.

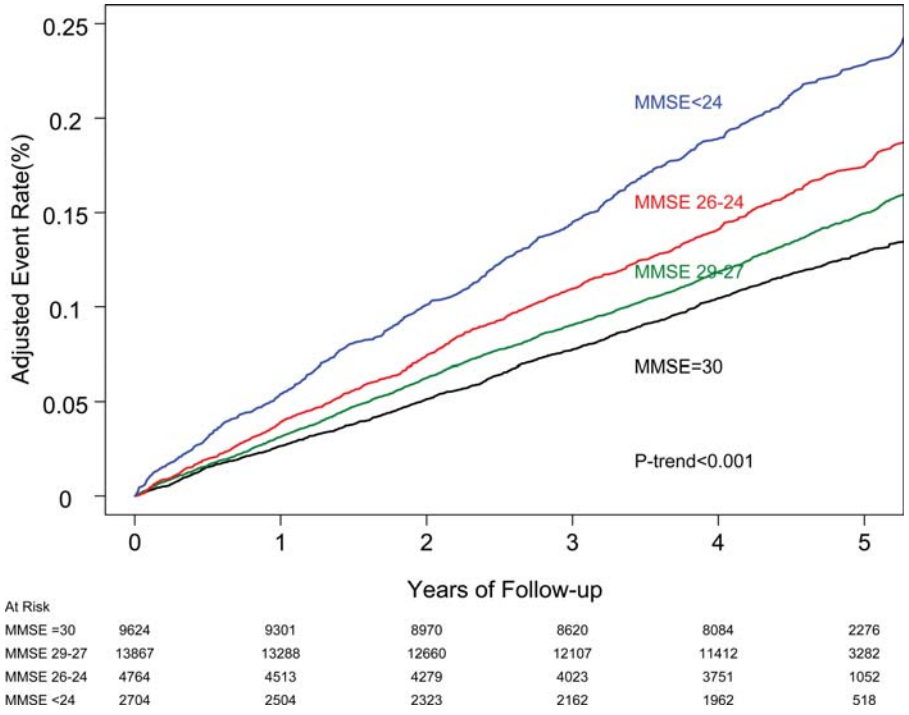

Figure 1 Kaplan–Meier Curve for hazard of composite of cardiovascular death, stroke, myocardial infarction and hospitalization for congestive heart failure, categorizes by the baseline Mini-Mental State Examination score. Black line represents those with a baseline MMSE = 30; Green line represents those with a baseline Mini-Mental State Examination of 29–27, red line represents those with a baseline MMSE = 26–24, and blue line represents those with baseline MMSE <24.

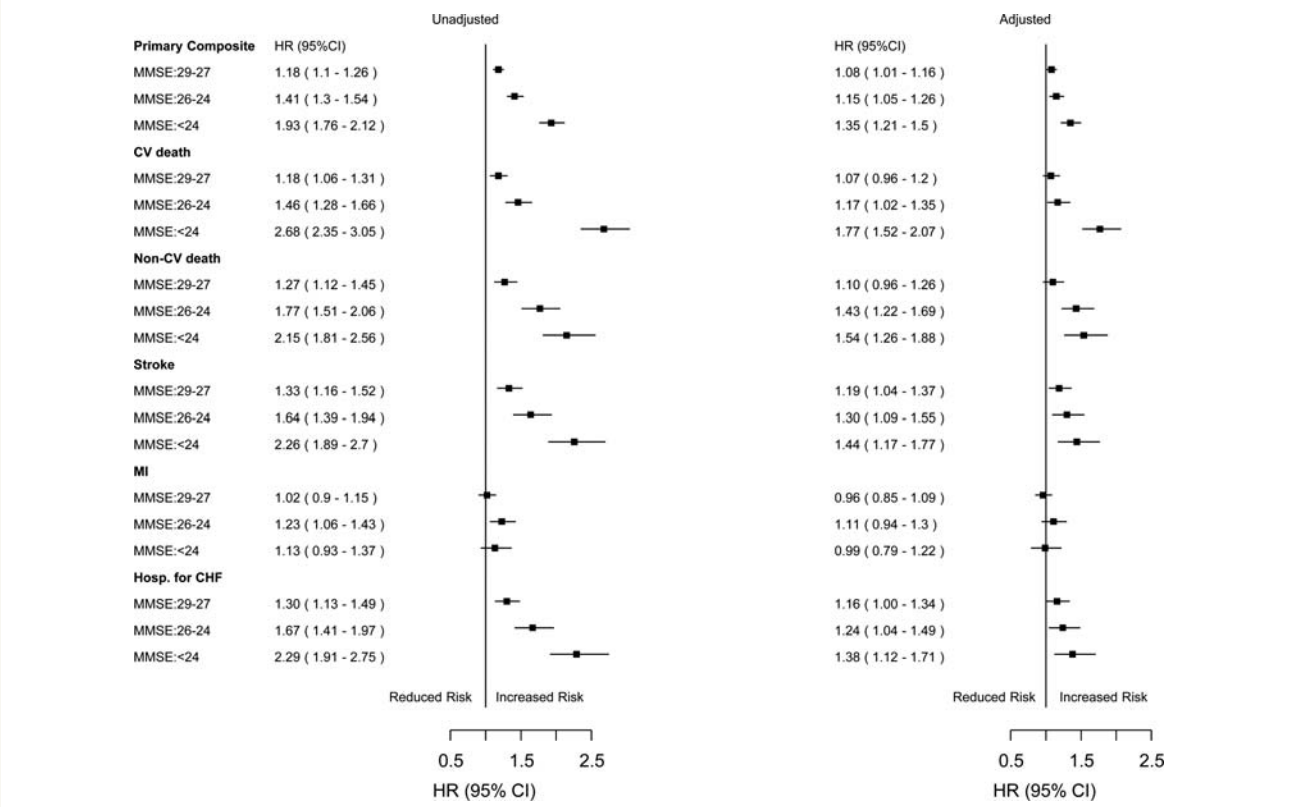

Figure 2 Two Forest plots for unadjusted and adjusted Cox models (hazard ratios and 95% confidence intervals) for the association between baseline Mini-Mental State Examination (categorized into baseline scores of 30, 29–27, 26–24, and <24, where 30 is the reference category) and cardiovascular death, non-cardiovascular death, stroke, myocardial infarction, and hospitalization for congestive heart failure. Adjusted analyses includes the following variables in multivariate model: age, sex, education, English-speaking, region, prior history of stroke or myocardial infarction and creatinine clearance, co-morbid vascular risk factors (hypertension, diabetes mellitus, glucose, LDL, HDL, smoking, atrial fibrillation), cardiovascular medications (β-blockers, Ca antagonists, diuretics, statin, ACE-inhibitor, anticoagulant, and antiplatelet), fruit and vegetable consumption; exercise, alcohol intake pattern, baseline blood pressure and change in blood pressure from baseline to final follow-up, depression, and psychosocial stress.

history of CVD, the association between MMSE score and the composite outcome was consistent with the overall results [MMSE score of 29–27 (HR: 1.28; 95% CI: 0.98–1.68), 26–24 (HR: 1.50; 95% CI: 1.09–2.08), and <24 (HR: 1.74; 95% CI: 1.21–2.48) vs. MMSE 30]. In the multivariable model, adjustment for depression, psychosocial stress, fruit and vegetable intake, pattern of alcohol intake and level of physical activity did not materially influence the magnitude of risk associated with the baseline MMSE score (*Table 3*). In addition, we did not find a significant interaction between MMSE and any of the following variables for any of the outcome measures: age, previous history of hypertension and baseline blood pressure, formal education level, previous history of stroke, alcohol intake pattern, depression, psychosocial stress, fruit and vegetable intake, and level of physical activity.

Mini-Mental State Examination domains and risk of cardiovascular events

For the composite outcome of all-cause death, stroke, myocardial infarction and hospitalization for congestive heart failure, orientation to place (HR: 1.52; 95% CI: 1.25–1.85), attention and calculation (HR: 1.10; 1.02–1.18), recall (HR: 1.10; 1.04–1.16), and design copy (HR: 1.15; 1.06–1.24) were significant predictors. *Table 4* details the association between MMSE domains and CV mortality, non-CV mortality, stroke, myocardial infarction, and hospitalization for heart failure.

Change in Mini-Mental State Examination score and risk of cardiovascular events

Between baseline and follow-up MMSE, 4559 participants had a decline of 2 points or more in the MMSE score. In the period after follow-up MMSE testing, the composite outcome was reported in 552/4559 (12.1%) 1936/22 007 (8.8%) of those without a decline in MMSE. On multivariable analyses, we found an association between decline in MMSE score (2 points) and risk of composite outcome (HR: 1.30; 1.18–1.44), CV death (HR: 1.47; 1.29–1.69), non-CV death (HR: 1.53; 1.30–1.80) and stroke (HR: 1.34; 1.11–1.61) and strong trend for increased risk of myocardial infarction (HR: 1.19; 0.99–1.43), and hospitalization for CHF (HR: 1.20; 0.99–1.46).

Table 3 Cox multivariable regression analyses

Variables in model		CV mortality	Non-CV mortality	Stroke	CHF hospitalization
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Univariate (MMSE)	MMSE 29–27	1.18 (1.06–1.31)	1.27 (1.12–1.45)	1.33 (1.16–1.52)	1.30 (1.13–1.49)
	MMSE 26–24	1.46 (1.28–1.66)	1.77 (1.51–2.06)	1.64 (1.39–1.94)	1.67 (1.41–1.97)
	MMSE <24	2.68 (2.35–3.05)	2.15 (1.81–2.56)	2.26 (1.89–2.70)	2.29 (1.91–2.75)
+Age, sex, English-speaking, education, region, prior vascular event,[a] vascular risk factors and medications,[b] initial BP, and Δ BP[c]	MMSE 29–27	1.07 (0.95–1.19)	1.10 (0.96–1.26)	1.19 (1.04–1.37)	1.15 (0.99–1.32)
	MMSE 26–24	1.19 (1.04–1.37)	1.46 (1.24–1.72)	1.32 (1.11–1.57)	1.25 (1.05–1.50)
	MMSE <24	1.87 (1.61–2.18)	1.61 (1.32–1.96)	1.48 (1.21–1.82)	1.43 (1.16–1.77)
Fruit and vegetables,[d] exercise,[e] depression, alcohol intake pattern,[f] psychosocial stress (final multivariable model)	MMSE 29–27	1.07 (0.96–1.20)	1.10 (0.96–1.26)	1.19 (1.04–1.37)	1.16 (1.00–1.34)
	MMSE 26–24	1.17 (1.02–1.35)	1.43 (1.22–1.69)	1.30 (1.09–1.55)	1.24 (1.04–1.49)
	MMSE <24	1.77 (1.52–2.07)	1.54 (1.26–1.88)	1.44 (1.17–1.77)	1.38 (1.12–1.71)

HR, hazard ratio.
[a]Previous MI, stroke/TIA and creatinine clearance.
[b]Hypertension, diabetes mellitus, glucose, LDL, HDL, smoking, atrial fibrillation, BMI, β-blockers, Ca antagonists, diuretics, statin, ACE-inhibitor, anticoagulants and antiplatelet.
[c]Baseline BP, treatment allocation, change in BP.
[d]Based on food frequency questionnaire.
[e]Based on estimated daily exposure.
[f]Never/former, current (moderate), current (binge).

Discussion

In this pooled analysis of two very large cohorts of people at increased CV risk, we found a graded, inverse association between baseline MMSE score and risk of stroke, hospitalization for congestive heart failure and death. The relationship was independent of all other measured prognostic factors. An MMSE score of <24/30 was associated with a 35% relative increase in risk of CV events, comparable with the risk conferred by a prior history of stroke or myocardial infarction. Within MMSE domains, impairments of orientation to place, attention-calculation, recall, and design copy were the strongest predicators of CV events and mortality. We also observed an association between changes in MMSE score and risk of CV outcomes.

Findings from prior studies examining the association between cognitive function and CVD have been inconsistent, and have primarily focused on stroke risk alone rather than all individual CV events.[2–8] Five studies[2,4,9,11,12] evaluated the association between cognitive impairment (mostly MMSE score) and CV events, of which, three[4,11,12] reported a significant association. Most studies[2–8,10,11] evaluated the association between cognitive testing and stroke, with five studies reporting a significant association. An analysis of the ADVANCE trial also reported an association between MMSE score and risk of CV events, although the population was confined to patients with diabetes mellitus.[12] Our study represents that largest cohort to evaluate the association between cognitive impairment and major vascular events, includes a broader spectrum of patients at increased CV risk, and our analysis adjusted for a larger number of lifestyle risk factors that may confound or modify the association. In addition, we provide novel information on the association between change in MMSE score and risk of CV outcomes.

It is likely that a reduced MMSE score is mostly a marker for covert cerebrovascular disease,[4,8] and we believes that two key observations support this contention.[28] First, we found that baseline MMSE had the strongest association with stroke, while it did not predict admission for myocardial infarction or unstable angina. Previous studies have shown that a prior history of clinical stroke is a much stronger predictor of recurrent stroke than myocardial infarction.[29] Secondly, the cognitive domains in the MMSE that were the strongest predictors of stroke and CV death have been reported to be preferentially associated with progression from preclinical to established vascular dementia, namely orientation to place, recall, and attention.[30] In addition, impairments in executive function, which are preferentially affected in early vascular cognitive decline,[31] are expected to impair completion of copy design on the MMSE. In effect, MMSE score might be considered comparable with creatinine clearance, left ventricular function, or ankle-brachial index, providing surrogate evidence of subclinical vascular disease. Although we do not have objective evidence of covert cerebrovascular disease with neuroimaging, we expect that such abnormalities were common in this cohort, given that one-fifth of patients had a previous history of clinical stroke, and epidemiological studies have shown that covert stroke occurs approximately four time more often than clinically overt stroke.[28] In addition, a prior history of clinical stroke was increasingly more common with progressive decline in MMSE, although the

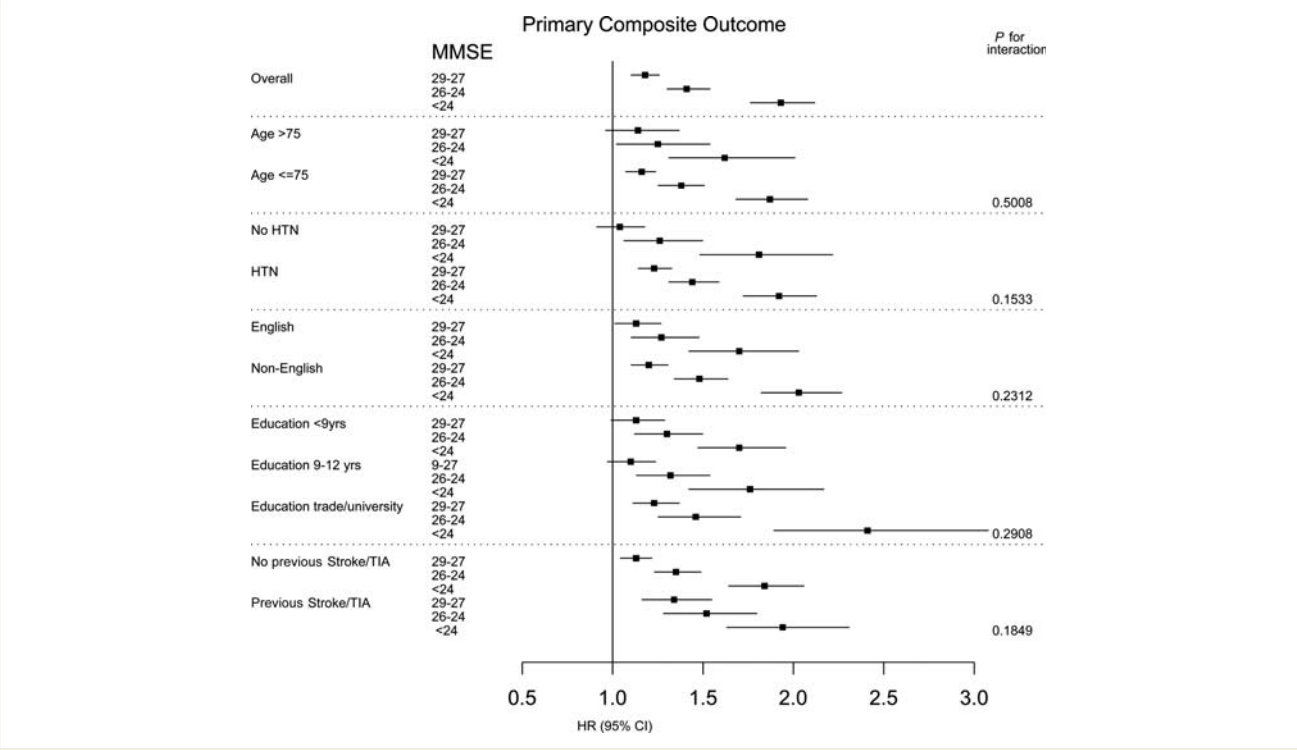

Figure 3 Univariate subgroup analyses by age (dichotomized into >75 and ≥75 years), previous history of hypertension, English-speaking and non-English speaking, and years of formal education (categorized into <9, 9–12 years, trade/university). Outcome measure is composite of cardiovascular mortality, stroke, myocardial infarction, and hospitalization for congestive heart failure.

Table 4 Association between Mini-Mental State Examination domains and major vascular events and mortality

	CV mortality	Non-CV mortality	Stroke	Myocardial infarction	Congestive heart failure
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Orientation (time)	1.44 (1.18–1.76)	1.16 (0.89–1.52)	1.10 (0.84–1.44)	0.93 (0.68–1.29)	0.97 (0.72–1.29)
Orientation (place)	1.31 (1.00–1.72)	0.78 (0.52–1.18)	1.62 (1.16–2.28)	1.22 (0.79–1.89)	1.45 (1.00–2.10)
Registration	1.06 (0.85–1.33)	1.13 (0.86–1.50)	0.71 (0.50–1.01)	0.97 (0.70–1.36)	1.14 (0.85–1.52)
Attention and calculation	1.14 (1.02–1.26)	1.12 (0.98–1.27)	1.15 (1.01–1.31)	1.08 (0.94–1.23)	1.14 (1.00–1.31)
Recall	1.10 (1.00–1.20)	1.03 (0.92–1.15)	1.15 (1.03–1.29)	1.04 (0.94–1.15)	1.03 (0.92–1.15)
Naming and repetition	1.03 (0.91–1.16)	1.09 (0.93–1.26)	0.98 (0.83–1.15)	0.96 (0.81–1.13)	0.99 (0.84–1.17)
Comprehension	1.01 (0.83–1.22)	1.21 (0.97–1.52)	1.01 (0.78–1.31)	1.10 (0.85–1.42)	0.88 (0.67–1.15)
Reading	0.95 (0.77–1.17)	0.93 (0.71–1.22)	1.03 (0.78–1.35)	0.99 (0.74–1.33)	0.94 (0.72–1.24)
Writing	1.04 (0.89–1.21)	1.26 (1.05–1.50)	0.85 (0.70–1.04)	1.14 (0.94–1.39)	1.35 (1.12–1.63)
Copying	1.30 (1.16–1.46)	1.12 (0.97–1.30)	1.23 (1.06–1.42)	1.02 (0.88–1.20)	1.14 (0.98–1.33)

Orientation to time (5 points; 4–5 = ref), orientation to place (5 points; 4–5 = ref), registration (3 points; 3 = reference), attention and calculation (5 points; 4–5 = reference), recall (3 points; 3 = reference), naming and repetition (3 points; 3 = reference), comprehension (3 points; 3 = reference), reading ability (1 point; 1 = reference), writing ability (1 point; 1 = reference), and design copy (1 point; 1 = reference).

association between MMSE score and CVD events was evident in those with and without a history of stroke or TIA (*Figure 3*).

A number of epidemiological studies have reported a consistent association between mild cognitive impairment and increased risk of mortality in community-dwelling persons.[32–36] In our population of patients at an increased CV risk, we found that impairments in cognitive testing increased the risk of both CV and non-CV causes of death, even for very modest reductions in the MMSE score. Most of the excess mortality was attributed to CV causes of death (*Table 2*). Within non-CV causes of death, infection and respiratory causes appeared to have the strongest association with cognitive impairment, while we did not observe an association

with deaths from cancer, injury, or neurological causes other than stroke. Certainly, the increased risk of respiratory infections may reflect an increased risk of aspiration which is known to be increased in patients with dementia. In addition, we found that a decline in the MMSE score from baseline to first follow-up was associated with an increased mortality, after adjusting for the baseline MMSE score.

We explored whether lifestyle behaviours, known to be more prevalent in patients with cognitive impairment, may explain the association between impaired cognitive testing and CV events. In particular, we evaluated the influence of dietary intake of fruit and vegetables, alcohol consumption, and exercise. Since these factors are potentially modifiable, understanding their contribution to the association between cognition and CV events is of clinical importance. Similarly, we also suspected that concomitant depression or psychosocial stress may confound the association, since both have been shown to increase the risk of CV disease and are common co-morbidities in patients with cognitive impairment. While most conditions were more common in patients with reduced MMSE score (*Table 1*), adjusting for these factors had only a very modest influence on the magnitude of the HR for the MMSE score (*Table 3*) after adjustment for age, sex, and vascular disease and risk factors. Although we were unable to present information on socioeconomic status, which has been previously reported to be a confounding factor,[9] we did not find the years of education to be a significant modifier of the association (*Figure 3*).

Our findings suggest that simple cognitive screening test, used commonly by general practitioners, identifies patients at an increased risk of stroke and CV death. As such, patients with impaired cognitive testing, especially in strategic domains, require aggressive vascular risk factor modification, similar to other secondary prevention populations. However, further research is required to determine whether routine cognitive screening in patients with CV disease improves clinical outcomes. In addition to cognitive domains measured by the MMSE, other cognitive domains, poorly measured by the MMSE, are also expected to be important. In particular, impairment in executive function is a prominent, often disabling, manifestation of early vascular cognitive impairment that has also been associated with increased mortality[37,38] and stroke risk in some studies. A recent study found that impaired subcortico-frontal activity, as measured by the Trails Making Tests (A and B), but not MMSE, predicted future risk of stroke.[8] Another study reported that measures of reasoning and vocabulary, but not memory and verbal fluency were associated with risk of coronary heart disease in people without CV disease.

Our study has a few limitations. First, our study cohort included patients at increased CV risk, included in a large randomized controlled trial. Accordingly, it is uncertain whether our results are applicable to other populations at lower CV risk. In particular, additional research is required to determine whether our findings may be extended to populations without evidence of overt CV disease. Secondly, most confounders (e.g. depression) were measured at a single time-point, and may not accurately reflect changes in these factors during the course of the trial. In addition, we did not use validated scales for some patient-reported measures, such as depression and psychosocial stress. Moreover, we cannot adjust for other potential confounders not measured in the current study. Thirdly, the MMSE is a screening test, and a relatively crude measure of cognitive function, especially for those with mild cognitive impairment.[39] Therefore, we are unable to comment on the effects of more subtle vascular cognitive dysfunction, especially deficits in executive function, as detailed. However, using the MMSE could also be argued to be a major strength of the study, since it is the most widely used cognitive screen in clinical practice and clinical research, making our findings interpretable to a wide audience. Further strengths of our study include the extremely large number of patients and events included in the analysis, the international distribution of the cohort, high completeness of data for MMSE and outcome measures, central adjudication of outcome events, and the availability of detailed covariates that could be used to adjust for a broad range of potential confounders. To our knowledge, the current study represents the largest cohort of people with CV disease and cognitive testing.

In conclusion, impaired cognitive testing with the MMSE is associated with a graded increase in the risk of stroke, CV death, and hospitalization for heart failure in population of patients at increased CV risk. An MMSE <24 confers a similar magnitude of risk as a previous history of clinical stroke. A simple cognitive screen provides important prognostic information in patients with a high CV risk.

Authors' contributions

All authors contributed to the discussions and interpretation of the data, and to the writing of the report. The analysis was planned by M.O'D., K.T., and S.Y., data were analysed by P.G. All authors had full access to data. No medical writer or other people were involved in the design, analysis, or writing of this manuscript. A full list of all investigators has been published.[21,22]

Conflict of interest: K.T., C.A., P.S., A.D., J.P., and S.Y. report receiving consulting and lecture fees and research grants from Boehringer Ingelheim and from other companies manufacturing angiotensin receptor blockers. The other authors declare no conflicts of interest. The sponsor of the trial was Boehringer-Ingelheim who had no role in data collection, analyses or the decision to submit for publications. The Steering Committee designed and oversaw the trial. All data were received, checked, and analysed independently at the coordinating centre at McMaster University. An Operations Committee, with representatives from McMaster University; its sub-offices at Oxford University, and the University of Auckland, Auckland, and the sponsor met regularly. The decision for the present analysis was made by members of the Steering Committee.

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