ASCEND (A Study of Cardiovascular Events iN Diabetes)

Cognitive Study

Design and Data Analysis Plan

1. Background

1.1 The ASCEND study

ASCEND is a mail-based randomized trial which aims to determine whether 100 mg daily aspirin and/or supplementation with 1 g capsules containing 90% omega-3 fatty acids (FA: 0.46g eicosapentaenoic acid [EPA], 0.38g DHA) daily prevents cardiovascular events in patients with diabetes who do not already have clinically manifest arterial disease (without leading to significant bleeding or other adverse events). The study design is a 2x2 factorial placebo-controlled randomized trial, in which, between 2005 and 2011, 15,480 participants have been randomly allocated to aspirin or placebo, and separately to omega-3 FA or placebo and followed for an average of 7.4 years.[1] Follow-up is predominantly mail-based, but with additional information about death, cancers and hospital admissions from central registries. The Protocol and Data Analysis Plan for the main study have been published previously.[1, 2]

1.2 Potential of ASCEND for investigation of cognitive outcomes

Dementia and cognitive impairment present major health care and social burdens which are increasing globally with increasing lifespan.[3] In observational studies, diabetes is associated, not only with a 2-3 fold increased risk of vascular events,[4] but also with a 50% increased risk of dementia[5] and a 20% increase in the rate of cognitive decline.[6 7, 8] Therefore, it is of particular importance to obtain randomized evidence of the effects of therapies for vascular prevention on cognitive decline among people with diabetes. Furthermore, the higher risks of cognitive decline and dementia among people with diabetes make them a potentially powerful population for investigating cognitive effects. The long mean follow-up of 7.4 years in ASCEND is a further strength of the ASCEND study to investigate cognitive outcomes.

Daily low dose aspirin is widely used in cardiovascular disease prevention to lower coronary, ischaemic stroke and transient ischaemic attack (TIA) risk. Typically aspirin reduces risk by about 12-25% but it is also associated with some risk of serious bleeding.[9] Cerebrovascular events, such as TIAs and strokes, and microbleeds in the brain are associated with cognitive impairment and dementia.[10-16] With population trends towards lower cardiovascular risks and increasing longevity, it is important to evaluate any effects of aspirin on cognitive function and dementia. Some benefit on cognitive function might be expected from the prevention of strokes and TIAs but randomized verification of a net benefit would be valuable. Alternatively, if aspirin caused microbleeds in the brain and materially adversely affected cognitive function (such as by increasing the rate of cognitive decline by 20%) this might alter the balance in assessing which risk categories of patient would benefit from aspirin.[17] Previous randomized trials of aspirin have not convincingly detected any effect on cognitive function but this has only been assessed in a total of about 10,000 participants and studies have had limited ability to allow adequately for lack of response to undertaking cognitive assessment, which would be associated with cognitive impairment.[18, 19]

Observational studies have demonstrated an association between high intake of oily fish (rich in omega-3 FA) and lower risk of cognitive impairment.[20] Numerous potential

mechanisms by which omega-3 FA (particularly DHA) could be neuro-protective have been suggested.[21] Several randomized trials have failed to demonstrate a beneficial effect of supplementation with omega-3 FA on cognitive function.[22-25] However, these studies may have been underpowered to detect small, but worthwhile clinically important, effects.

2. ASCEND Cognitive Study

The initial design of the main ASCEND trial did not include cognitive testing but funding was sought and obtained in 2016 from Alzheimer's Research UK to conduct cognitive testing. Initial ethics committee (MREC 03/08/087) approval for the ASCEND study was obtained in 2003 and approval for a substantial amendment for a cognitive study was obtained in December 2016. The aim of the ASCEND Cognitive Study is to determine whether the ASCEND aspirin and omega-3 FA study treatments, separately, have a net benefit or adverse effect on dementia and cognition.

2.1 Assessment of cognitive function at the end of ASCEND

It was planned to assess cognitive function in all participants in the ASCEND trial who remained on active follow-up at the final study assessment (i.e., the approximately 12,000 surviving participants who were not on GP follow-up). Participants are invited to complete the cognitive assessment in one of two ways. Those who provide a valid e-mail address are invited to complete the online "Healthy Minds" cognitive function test developed by UK Biobank. Those who do not complete the online assessment receive a telephone call from a study nurse who administers the Telephone Interview of Cognitive Status (TICS-m) questionnaire[26] and the verbal fluency (VF) test.[27]

The online cognitive function test ("Healthy Minds") is a recently developed battery of cognitive function tests that has been used to assess 100,000 healthy adults enrolled in the UK Biobank study.[28] All tests have been constructed using established testing paradigms that have been shown to produce valid scores and to be acceptable to participants.[29] The Healthy Minds online cognitive function assessment used for ASCEND includes 5 tests given in the order: (i) fluid intelligence; (ii) trail making; (iii) symbol-digit substitution; (iv) pairs matching; and (v) numeric memory.[30] Participants may abandon an individual test (which might indicate they found it difficult) and proceed to the next test during the assessment. Hence, potentially informative partial data will be available for some participants. (In the UK Biobank study an additional reaction time test has been found to be unreliable and so this test was not included in ASCEND.)

The TICS-m is a 13-item test covering four component domains: orientation, memory (registration, recent memory and delayed recall), attention/calculation and language (semantic memory, comprehension and repetition); test score ranges are from 0-39 with a higher score indicating better cognitive function. In the VF test participants are asked to name in one minute as many animals as they can and the score is the number of different animals named.

Both a Healthy Minds cognitive function derived score and a TICS-m-based score have previously been shown to be associated with prior disease (the Healthy Minds score with cardiometabolic diseases in UK Biobank,[31] and the TICS-m-based score with in-trial cerebrovascular and cardiac events and new diabetes among 45,000 participants in the HPS, SEARCH and HPS2-THRIVE trials[32]) and with age. A score based on TICS-m and VF

in these trials decreased at a rate of about 4% of a standard deviation per year of age above 60.

2.2 Capture of cognitive impairment and dementia

Dementia or cognitive impairment is captured from multiple sources in the ASCEND trial: during routine trial follow-up, participants were asked to record all serious illnesses and hospitalisations (including dementia or cognitive impairment); at final participant follow-up, participants are asked whether they have been referred to a memory clinic; additionally participants may state that they are unable to complete cognitive assessment because of cognitive impairment, or use of dementia drugs may be recorded; at final GP follow-up, dementia or cognitive impairment was specifically asked about; linked electronic Hospital Episode Statistics (HES) data and mortality data, provides an additional source of evidence of dementia and indications of cognitive impairment. A study evaluating HES data as a source of dementia diagnosis concluded that there was good agreement with evidence from primary care records but a mean delay of 1.6 years between first mention of the condition in hospital admissions compared to in primary care records.[33] Therefore, diagnoses of dementia-related outcomes from HES data or from death certificates will be included up to 31 March 2019, a date 1.5-2 years beyond when cognitive assessment was sought (March-December 2017).

2.3 Definitions of dementia/cognitive impairment-related outcome

Dementia/cognitive impairment is defined as:

- Dementia or cognitive impairment recorded on follow-up form; or
- Taking dementia medications; or
- Dementia ICD-10 diagnosis (Alzheimer's, vascular and unspecified, Appendix Table A1*) in HES or recorded on death certificate; or
- Referral to memory clinic recorded on final follow-up form; or
- Cognitive impairment cited as a reason for not completing cognitive assessment; or
- Confusion or disorientation recorded on follow-up form; or
- Confusional state/delirium ICD-10 diagnosis (Appendix Table A1*) in HES or recorded on death certificate; or
- Senile degeneration of brain/unspecified degenerative disease of nervous system ICD-10 diagnosis in HES or recorded on death certificate (Appendix Table A1*)
- Discharge referral to geriatric psychiatry.

(* In combination, these correspond to all ICD-10 codes in Appendix Table A1)

Additional outcomes that will be considered in exploratory and long-term analyses include (i) dementia/cognitive impairment defined by any of the first three categories above and (ii) adding discharge destination of 'care home' on any HES episode to the above definition.

2.4 Definitions of cognitive score outcomes

The main comparisons of the TICS-m-based and Healthy-Minds-based cognitive tests are based on Z-scores.

From the 5 Healthy Minds tests, 13 metrics and 5 binary flags to indicate completion of the tests are used (Table A2). As abandoning a test could be an indication of having difficulty, and hence be informative, the approach tries to include partial information as far as

possible. Participants are regarded as having attempted the testing if they complete at least one test or provide usable partial data on at least two tests. For participants who attempt testing, a principal component analysis is conducted over the 18 items of data from the tests, as a data reduction technique. The first principal component (signed so that a higher value indicates better cognitive function) can be regarded as a measure of general cognitive function and is taken as the score.[34] (This has mean zero and standard deviation of one and so is a Z-score).

For the TICS-m based score separate Z-scores for TICS-m and VF will be computed by subtracting their mean and dividing by their standard deviation and forming a weighted average of the two Z-scores with weights 4:1 to reflect the 4 domains covered by TICS-m.

3. ASCEND Cognitive Study: Data Analysis Plan

3.1 *Randomized comparisons to 31 March 2019*

All comparisons will involve comparing outcomes available from date of randomization until 31 March 2019 among all those participants allocated at randomization to receive aspirin or, respectively, omega-3 FA daily versus all those allocated to receive matching placebo, within any specified subgroup, but regardless of whether the participant continues on study treatment or not (i.e. “intention-to-treat” analyses).

The primary outcome in the ASCEND Cognitive Study is:

I The first recorded incidence of dementia/cognitive impairment (as defined by conditions specified in 2.3).

The secondary outcome in the ASCEND Cognitive Study is:

II Cognitive Z-score among participants who attempted cognitive testing, with adjustment for age at cognitive test and sex.

Further exploratory investigations will assess the effects of the study treatment assignments on the additional outcomes mentioned in 2.3 and on non-response to cognitive testing. Study average adherence to study treatment (over the whole study) will be taken into account in the interpretation of results.

3.2 *Statistical Power*

Preliminary blind data suggest that 1000-1200 participants in total may have the dementia/cognitive impairment outcome I. Power calculations for outcomes I and II have been tabulated under the assumption that about 6.5% of participants in the assignment arm with lower risk of the dementia/cognitive impairment outcome with suffer such an event and that 9000 participants undertake cognitive testing (see Appendix for details of calculations). The study has >80% power at 2P<0.05 to detect a decrease in dementia risk of 15% or an increase in dementia risk of 18% (Table A3). It also has power >80% at 2P<0.05 to detect a 20% change in cognitive ageing.

3.3 *Long-term follow-up of the effects of aspirin*

The main ASCEND study includes long-term follow-up of the effects of aspirin on its main outcomes. In parallel, analyses of the effects of aspirin on cognitive outcomes are planned for 5 and 10 years after the end of the scheduled treatment period (i.e., including data up to

31.3.2022 and 31.3.2027). These will involve intention-to-treat comparisons of outcome I and of the narrower and broader dementia/cognitive impairment outcomes specified in 2.3, among all those previously allocated aspirin compared with those previously allocated placebo.

3.4 *Details of analyses*

Outcome I and other dementia/cognitive impairment outcomes
The "logrank" test[35, 36] will be used to calculate average event rate ratios, confidence intervals, and two-sided P-values.

Outcome II
The effects of treatment on the TICS-m-based and Healthy minds Z-scores will be estimated separately with adjustment for age (as single year categories) and sex, and then combined in an inverse-variance fixed effects meta-analysis. (In general, participants do not undertake both types of cognitive test, but if this occurs the earlier will be used.)

The results of the primary comparisons for aspirin and for omega-3 FA will be considered statistically significant if the 2-sided P-value is <0.05.

Allowance for multiple comparisons in secondary and exploratory analyses
No formal adjustment to P-values and confidence limits for the multiplicity of testing in secondary and exploratory analyses will be made, but allowance will be made in the interpretation of their results (by requiring more extreme P-values to infer evidence of effect in such analyses).
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Appendix

Table A1: International Classification of Disease (ICD-10) codes used for dementia/cognitive impairment and indications of cognitive impairment

ICD-10	Dementia/cognitive impairment
	Alzheimer's disease
F00	Dementia in Alzheimer's disease
F000A	Dementia in Alzheimer's disease with early onset
F001A	Dementia in Alzheimer's disease with late onset
F002A	Dementia in Alzheimer's disease, atypical or mixed type
F009A	Dementia in Alzheimer's disease, unspecified
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer disease, unspecified
G30.9	Alzheimer's disease unspecified
	Vascular dementia
F01	Vascular dementia
F010	Vascular dementia of acute onset
F011	Multi-infarct dementia
F012	Subcortical vascular dementia
F013	Mixed cortical and subcortical vascular dementia
F018	Other vascular dementia
F019	Vascular dementia, unspecified
I67.3	Binswanger's disease
	Unspecified dementia type
F03X	Unspecified dementia
F051	Delirium superimposed on dementia
	Non-specific indications of cognitive impairment
F050	Delirium not superimposed on dementia, so described
F058	Other delirium
F059	Delirium unspecified
G31.1	Senile degeneration of brain, not otherwise classified
G31.9	Degenerative disease of nervous system, unspecified

Table A2: Test metrics and binary missing indicator flags in the Healthy Minds assessment

Data item	Partial information used
Fluid intelligence score	Y
Fluid intelligence number attempted	Y
Trail making time for round 1: inverse	Y
Trail making time for round 2: inverse	Y
Trail making score round 1: negative of number of errors	Y
Trail making score round 2: negative of number of errors	Y
Symbol-digit substitution number correct	Y
Symbol-digit substitution attempts made	Y
Pairs matching score for round 1: negative of number of errors	
Pairs matching score for round 2: negative of number of errors	
Pairs matching completed round 3*: binary flag	
Pairs matching score for round 3: negative of number of errors	
Numeric memory score (maximum number of digits remembered)	Y
Binary missing indicator flags for all data	
Fluid intelligence score complete	
Trail making complete	
Symbol-digit substitution complete	
Pairs matching complete	
Numeric memory complete	

* Pairs round 3 is offered only to participants making 0 or 1 error on round 2, hence indicator is regarded as a data item.

A1. Power calculations

The hypothesised effects of the interventions are expressed in terms of their percentage effects on the dementia/cognitive impairment outcome, their percentage effects on cognitive ageing and their corresponding effects on the cognitive function Z-score. Preliminary blind data suggest that the number of participants having the dementia/cognitive impairment outcome I maybe about 1000-1200. Therefore, the power calculations for a decrease in risk of dementia are based on assuming that the number of participants in the placebo arm having the dementia/cognitive impairment outcome I is 600 (7.8%); power calculations for an increase in risk of dementia assume that the number of participants in the placebo arm having the dementia/cognitive impairment outcome I is 500 (6.5%). (This difference is so that with risk differences of around 20%, the total numbers with the outcome remains around 1100.) We assume that 9000 participants will complete cognitive testing.

The study has >80% power at 2P<0.05 to detect a decrease in dementia/cognitive impairment risk of 15% or an increase in dementia/cognitive impairment risk of 18%. It also has power >80% at 2P<0.05 to detect a 20% change in cognitive ageing (Table A3).

Table A3: Power of the study to detect different effects of the interventions

Primary outcome: dementia/cognitive impairment				
	N with event		**Power at**	**Power at**
Change in risk	**Active**	**Placebo**	**2P=0.05**	**2P=0.01**
-22%	468	600	99%	95%
-20%	480	600	97%	89%
-18%	492	600	92%	79%
-16%	504	600	85%	66%
-15%	510	600	80%	59%
22%	610	500	93%	80%
20%	600	500	88%	71%
18%	590	500	81%	60%
16%	580	500	71%	48%
15%	575	500	66%	42%
Secondary outcome: cognitive score				
Decrease or decrease in cognitive ageing	**Corresponding years of ageing and Z-score difference***		**Power at 2P=0.05**	**Power at 2P=0.01**
22%	1.6, -0.065		87%	69%
20%	1.5, -0.059		80%	59%
18%	1.3, -0.053		71%	48%
16%	1.2, -0.047		61%	37%
15%	1.1, -0.044		56%	32%

* In trial of 7.4 years, assuming cognitive score decline of 0.04 per year of age.