ASCEND: A Study of Cardiovascular Events in Diabetes

Heart failure outcomes in ASCEND (HF-ASCEND): an exploratory analysis of the effects of aspirin and omega-3 fatty acids on heart failure.

Data Analysis Plan

Contents

1. Version

Version	Date	Author	Description of changes
1.0	21.07.2022	Michelle Goonasekera	Initial version

2. Background

2.1. The ASCEND study

ASCEND was a mail-based randomised trial which aimed to determine whether 100mg daily aspirin and/or supplementation with 1g capsules containing 90% omega-3 fatty acids (FA: 0.46g eicosapentaenoic acid [EPA], 0.38g docosahexaenoic acid [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 was a 2x2 factorial placebo-controlled randomised trial, in which, between 2005 and 2011, 15,480 participants were randomly allocated to aspirin or placebo, and separately to omega-3 FA or placebo and followed for an average of 7.4 years.[1] The Protocol and Data Analysis Plan for the main study have been published previously.[1,2]

2.2. Potential role of aspirin and omega-3 fatty acids in heart failure

Observational studies have shown that individuals with diabetes mellitus (DM) have a 2- to 4-fold increased risk of heart failure (HF) and are also at higher risk of developing coronary artery disease, including silent myocardial infarctions (MI). [3-5] Coronary artery disease is the commonest cause of HF. Therefore, treatment of ASCEND participants with aspirin could lead to a reduction in the risk of coronary artery disease including silent MI and in turn reduce the long-term risk of developing HF.[6]

The role of omega-3 fatty acids (FA) in HF is less clear. The REDUCE-IT trial showed that among patients with established cardiovascular disease or diabetes and other risk factors on statins, with elevated triglyceride levels, over a median follow-up period of 4.9 years, icosapent ethyl 4g daily did not have a significant effect on the risk of HF compared to placebo (4.1% and 4.3% respectively).[7,8] The VITAL-HF study showed no difference in HF hospitalisations among patients without a history of cancer or cardiovascular disease randomised to 1g daily of omega-3 FA versus placebo (HR, 0.96 [95% CI, 0.80–1.14]), However, a post-hoc subgroup analysis of individuals with and without type 2 DM suggested a beneficial effect versus placebo in those with diabetes on first and recurrent HF hospitalisations. During a median follow-up of 5.3 years, among participants with type 2 DM at baseline, first HF hospitalisation occurred in 65/1784 participants allocated omega-3 FA (3.6%) and 90/1738 participants allocated placebo (5.2%) (HR: 0.69; 95% CI: 0.50-0.95). In participants without type 2 DM, first HF

hospitalisation occurred in 177/11053 allocated omega-3 FA and 164/11163 allocated placebo (HR: 1.09; 95% CI: 0.88-1.34, p interaction <0.019).[9,10]

No large randomised controlled trials have been conducted to address the possibility that aspirin may contribute to a reduction in the risk of HF in individuals with diabetes and no prior cardiovascular disease. The ASCEND trial presents a unique opportunity to conduct an analysis of randomised trial data to explore this important hypothesis.[11] It may also help consolidate the available evidence on the effects of omega-3 FA on HF.

2.3. Use of routinely collected healthcare data for heart failure outcome ascertainment

Ascertainment of HF events in cardiovascular trials is a complex process which could be streamlined to reduce the complexity and overall cost of trials and facilitate the better reporting of HF outcomes and the conduct of larger trials.[12,13] Routinely collected healthcare data (RCD) can be used to ascertain and adjudicate events to achieve this goal.[14,15] Outcomes can be identified solely from the presence of a single diagnostic code or a combination of codes (coding algorithms) in the routine dataset. However, review of individual RCD records by clinicians is straightforward and may increase the accuracy of events ascertained using these records. Therefore, this analysis will also include outcomes ascertained using coded hospital admission data and coded death certificate data by searching the databases using a code list. Outcomes identified will undergo both clinical adjudication using medical records and routine data based adjudication by clinician review of the routine data record.[16] Throughout the rest of this document the term RCD will refer specifically to hospital admission data and death certificate data.

3. Purpose

The purpose of this Data Analysis Plan is to describe the strategy, rationale and statistical methods which will guide assessment of the effect of aspirin and omega-3 FA on HF outcomes. Analyses and reports will be prepared by the coordinating centre in the Clinical Trial Service Unit, University of Oxford.

4. Plan of Investigation

4.1. Aims

The main aim of this analysis it to assess the effects of aspirin and omega-3 FA on the risk of HF hospitalisation or death in people with diabetes and no prior atherosclerotic disease.

4.2. Methods

A detailed description of methods is available in ASCEND Protocol Version 10.3_2021-05-06, Appendix 4 (Protocol Appendix 4) which is available in the ASCEND webpage. In brief, possible HF hospitalisations will be identified by directly searching hospital admission data from Hospital Episode Statistics (HES), Patient Episode Database Wales (PEDW) and the Scottish Morbidity Record (SMR) datasets combined with Office for National Statistics (ONS) death data using a list of International Classification of Diseases, 10th Revision (ICD-10) codes in any position, suggesting the presence of HF in RCD (RCD-reported events) (***Table 1***), and by searching the ASCEND study data base of study reported serious adverse events for HF read codes (study reported events). The cut-off dates for searching HES and other RCD sources for HF hospitalisations and deaths will be between randomisation and the 31st of July 2017. The main code search will include a group of HF specific codes and two codes not specific to HF (pulmonary oedema and cardiogenic shock). The HF outcomes of interest to be ascertained are (a) hospitalisations where HF is the primary reason for admission, or (b) hospitalisations where HF is a significant complication prolonging it (either separate to the primary event or resulting from it), and (c) deaths where the underlying cause of death is HF.

Wherever possible, study reported and RCD reported hospitalisations will undergo clinical adjudication, seeking additional information from participants' GPs (except study reported events that have already been clinically adjudicated). During clinical adjudication confirmed HF events will be assigned a sufficiency code Y or P. Y indicates that sufficient information has been provided to the adjudicating clinician to confirm the event. P indicates there is reason to believe that the event did occur, but there is insufficient information to fully adjudicate and no further information is going to become available.

All study and RCD reported events will also undergo RCD-based adjudication, by clinician review of the RCD records. During RCD-based adjudication it will be decided if an admission was related to acute decompensated HF rather than a record of pre-existing HF. A level of certainty will be assigned to each event using the sufficiency codes Y and P. Here, Y indicates definite HF and P, possible HF (see Protocol Appendix 4 for details). For both study-reported and RCD-reported events, HF hospitalisation will be classified as a) the primary reason for admission, or (b) a significant complication prolonging it (either separate to the primary event or resulting from it) during the adjudication process.

Events adjudicated as pre-existing HF will be coded as chronic HF and dated to the first appearance of HF in the RCD record (this maybe prior to randomisation).

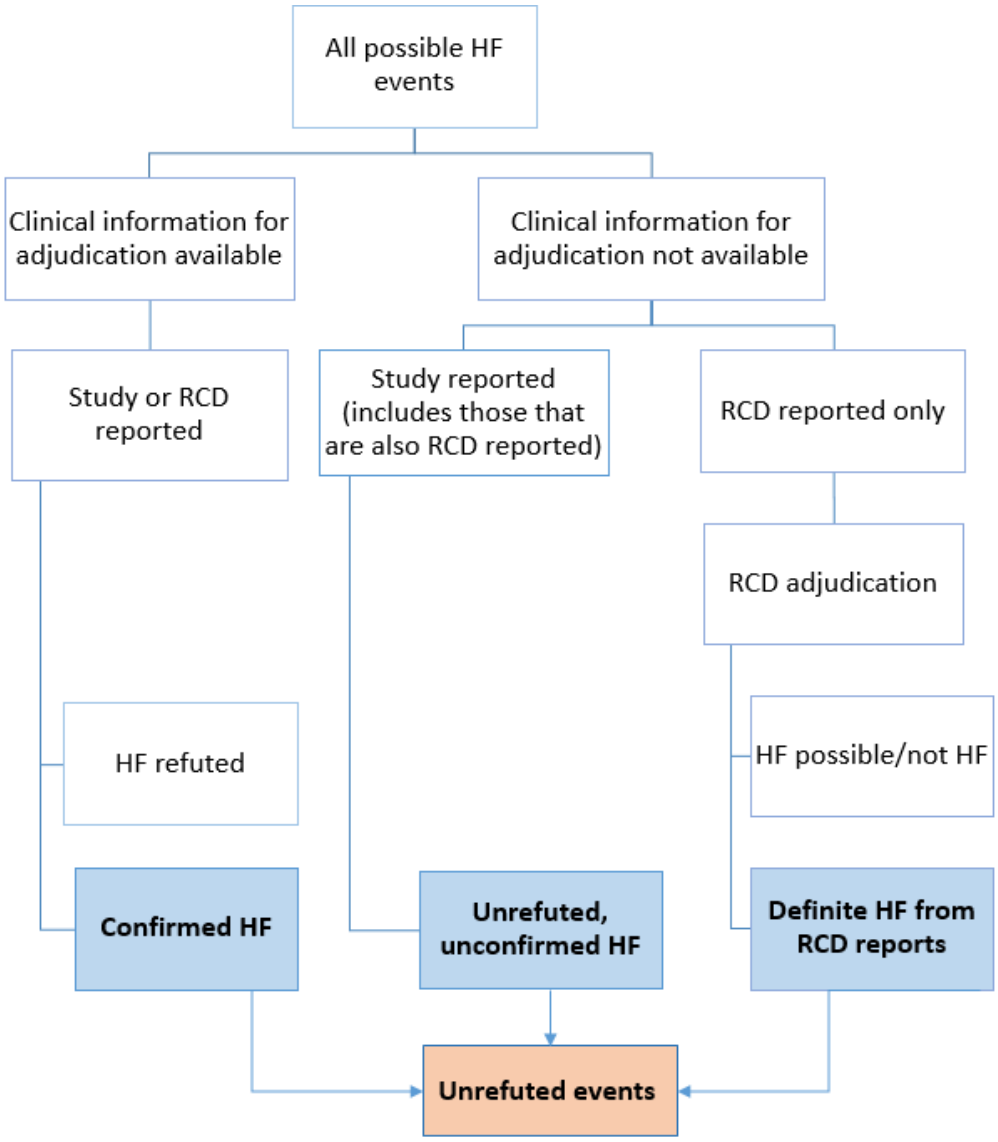
Table 1. ICD-10 codes used to identify heart failure from routinely collected data

ICD-10 code	Code Description
ICD-10 codes specific for heart failure and cardiomyopathy (narrow definition)	
I110	Hypertensive heart disease with (congestive) heart failure
I130	Hypertensive heart and renal disease with (congestive) heart failure
I132	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I255	Ischaemic cardiomyopathy
I42x	Cardiomyopathy
I42	Cardiomyopathy
I420	Dilated cardiomyopathy
I421	Obstructive hypertrophic cardiomyopathy
I422	Other hypertrophic cardiomyopathy
I423	Endomyocardial (eosinophilic) disease
I424	Endocardial fibroelastosis
I425	Other restrictive cardiomyopathy
I426	Alcoholic cardiomyopathy
I427	Cardiomyopathy due to drugs and other external agents
I428	Other cardiomyopathies
I429	Cardiomyopathy, unspecified
I43	Cardiomyopathy in diseases classified elsewhere
I43X	Cardiomyopathy in diseases classified elsewhere
I430	Cardiomyopathy in infectious and parasitic diseases classified elsewhere
I431	Cardiomyopathy in metabolic diseases
I432	Cardiomyopathy in nutritional diseases
I438	Cardiomyopathy in other diseases classified elsewhere
I50	Heart failure
I500	Congestive heart failure
I501	Left ventricular failure
I502	Systolic (congestive) heart failure
I503	Diastolic (congestive) heart failure
I504	Combined systolic (congestive) and diastolic (congestive) heart failure
I509	Heart failure, unspecified
I50X	Heart failure
ICD-10 codes that suggest underlying heart failure	
J81	Pulmonary oedema
R570	Cardiogenic shock

All deaths occurring during trial follow-up have undergone adjudication as part of the main trial analysis, based on clinical review of the ONS death certificate report and any other information available (including participant reported events and RCD relating to hospitalisations). However, when this process was undertaken, HF outcomes were not a main focus of the analysis and there may be some deaths where the RCD records suggest a death due to ischaemic cardiomyopathy, but the death has not been adjudicated as a HF death. These types of events may be re-coded using clinical review of the ONS death certificate reports and RCD records as part of this current analysis.

An exploratory intention-to-treat analysis will be undertaken of the effects of the randomised treatments on HF outcomes in all randomised participants. This randomised comparison will be undertaken using confirmed events from either source and unrefuted, unconfirmed events either reported in the study or classified as definite in the RCD (**Figure *1***).

Figure 1. Events included in the analysis based on event source and availability of clinical information for adjudication



Events included in the randomised comparison are all unrefuted events.

Confirmed HF *events are events that have been confirmed by clinical adjudication.* ***Unrefuted, unconfirmed HF*** *events are study-reported events (including those also RCD-reported) that have inadequate clinical information to confirm or refute the event.*
Definite HF from RCD reports *are unrefuted, unconfirmed events reported only in RCD that have been RCD adjudicated as definite HF.*

5. Data Analysis Plan

5.1. Randomised comparisons during the scheduled treatment period

All comparisons will involve comparing outcomes during the scheduled treatment period (i.e. from date of randomisation to date of death or censoring regardless of whether the participant continues on study treatment or not) among all those participants allocated at randomisation to receive aspirin (or, respectively, omega-3 FA) daily versus all those allocated to receive matching placebo (i.e. “intention-to-treat” analyses). Analyses will be of the first occurrence of the specified outcome. The same censoring rules defining the scheduled treatment period in ASCEND (see Data Analysis Plan which was included as a supplementary appendix with the ASCEND baseline paper)[2], which for participants not otherwise censored was until their final follow-up between January and July 2017, will be applied to this analysis with one exception: all individuals who have withdrawn consent for in-trial and/or long-term follow up will be censored at day zero.

All analyses in this section will be conducted using HF hospitalisations defined for the randomised comparison in section 4.2 (also shown in **Figure *1***) and adjudicated deaths due to HF.

5.1.1. Primary outcome

The primary outcome is the first unrefuted hospitalisation for new or worsening HF or death due to HF. This outcome includes:

- The first unrefuted hospitalisation for new or worsening HF (i.e., where HF is either the primary reason for admission or a significant complication prolonging it, either separate to the primary reason for admission or resulting from it).
- Deaths where the underlying cause of death is HF.

5.1.2. Secondary outcomes

Secondary outcomes include:

1. The first unrefuted hospitalisation for new or worsening HF (i.e., where HF is either the primary reason for admission or a significant complication prolonging it, either separate to the primary reason for admission or resulting from it).
2. Death where the underlying cause of death is HF.

5.1.3. Tertiary outcomes

Tertiary outcomes will include:

1. The first unrefuted hospitalisation for new or worsening HF, where HF is the primary reason for hospitalisation.

2. The first unrefuted hospitalisation for new or worsening HF, where HF was a significant complication prolonging the admission either separate to the primary event or resulting from it.

5.1.4. Pre-specified subgroup analyses

Pre-specified subgroup analyses of the primary endpoint will be done for some of the key prognostic variables included in the main ASCEND analysis including:

- Sex,
- Age at randomization (<60; ≥60 <70; ≥70 years),
- Duration of diabetes (<9; ≥9 years),
- Use of aspirin prior to randomisation,
- Vascular risk score (predicted 5-year risk of serious vascular events (SVE) without aspirin or omega-3 FA) – see main ASCEND Data Analysis Plan for derivation.[2]

5.2. Details of Analysis

5.2.1. Effects of allocation to aspirin and omega-3 fatty acids (main randomised comparison)

The “log-rank” based methods will be used to conduct time-to-event analyses of the first relevant events and calculate average event rate ratios, confidence intervals, and two-sided P-values.[17,18] Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). No allowance will be made for multiple hypothesis testing for the primary assessment, and results will be considered statistically significant if the 2-sided p-value is <0.05.

For the secondary and exploratory assessments, allowance in their interpretation will be made or multiple hypothesis testing. Tests for trend (or difference) in the proportional effect on particular outcomes across specific subgroups will be used (with allowance in the interpretation for multiple comparisons and for other differences between the subgroups) to determine whether the effects in those subgroups are clearly different from the overall effect (see the main ASCEND Data Analysis Plan for details).[2]

5.2.2. Study average compliance analysis

When assessing the effects of aspirin and omega-3 fatty acids on HF outcomes, the effect of full compliance with the treatment will be estimated based on the observed intention-to-treat effects on the HF outcomes and average in-trial compliance with the randomised treatment (determined by participant reports and treatment issue records). See main ASCEND data analysis plan for a detailed example.[2]

6. References

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