ASCEND: A Study of Cardiovascular Events in Diabetes

Louise Bowman

Senior Clinical Research Fellow
Clinical Trial Service Unit
University of Oxford, UK
ASCEND: The Research Question

ASCEND: A Study of Cardiovascular Events in Diabetes

• For people with diabetes who have not yet had a heart attack or stroke:
  – Is low-dose aspirin beneficial?
  – Are omega-3 fish oils beneficial?
  – Are these treatments safe?
The Study Design:

2x2 factorial design randomised trial of aspirin vs placebo and omega-3 FA vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Aspirin tablets</th>
<th>Placebo tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 FA</td>
<td>3750 Aspirin + Omega-3 FA</td>
<td>3750 Omega-3 FA</td>
</tr>
<tr>
<td>Placebo</td>
<td>3750 Aspirin</td>
<td>3750 Neither</td>
</tr>
<tr>
<td>capsules</td>
<td>7500 Aspirin</td>
<td>7500 Neither</td>
</tr>
<tr>
<td></td>
<td>7500 Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Aspirin tablets: 7500
Placebo tablets: 7500

- Omega-3 Fatty acids (FA) capsules
- Placebo capsules

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin tablets</td>
<td>3750</td>
<td>3750</td>
</tr>
<tr>
<td>Placebo tablets</td>
<td>3750</td>
<td>3750</td>
</tr>
</tbody>
</table>

- Aspirin 7500
- Placebo 7500
The Problem
The Solution

- Streamlined
- Cost effective
- Simple eligibility criteria
- Mail-based trial design
No study clinics required
The Funding

- British Heart Foundation special project grant £2.7 million
- Bayer/Abbott: study drug and funding for packaging
Trial coordination

• Sponsor: University of Oxford
• Steering Committee
• Independent Data Monitoring Committee
The Next Problem

• Identification of potentially eligible study participants
  
  – Central databases
    • Hospital-based registers
    • Regional registers (eg retinopathy screening)

  – Other approaches
    • Invited direct from GP
    • Self-nominate/friends & family
Central recruitment: invitations sent to potentially eligible patients

• Patients mailed
  – Invitation letter (from lead clinician)
  – Information leaflet
  – Screening questionnaire
  – Consent form

• 24 hour telephone service to deal with any questions about the study
I have read and understood the leaflet “ASCEND: Invitation to join a large medical research project”.

- I have had an opportunity to telephone the Freephone number 0800 5853235 and ask any relevant questions. All my questions have been answered by my study OR I decided that I did not need to ask any questions.
- I understand that my participation in the ASCEND study is voluntary and that I am free to withdraw from the study at any time without my medical care or rights being affected.
- I understand that information about my progress in the ASCEND study will be recorded on a computer database, and that these data will be stored securely and confidentially on a computer at Oxford University.
- I agree that information about any serious illnesses (such as heart attacks, strokes or cancers) may be supplied in confidence to the study co-ordinators by my own doctors and by NHS and other central registries for use in the ASCEND study.
- I agree that my hospital and other medical records may be accessed in confidence by authorised individuals from the ASCEND study and by regulatory authorities to check the study is being carried out correctly.
- I understand that my GP will be informed about the provisional agreement to participate in the ASCEND study and that in about 2 month’s time I will have another opportunity to decide whether or not I want to join the long term part of the study.

I am happy to take part in ASCEND:

Signature: 

A PRINTED name: 

Today’s date: 

Please check that you have answered every question, and signed and dated the form.

Return the completed form in the Freepost envelope.

Freepost RL1U-TKES-SURB, ASCEND, Old Road Campus, Headington, Oxford OX3 0LZ.

If you have any questions about this study, call the Freephone number 0800 5853235 (preferably during working hours).

If this questionnaire indicates that you are eligible to take part in the ASCEND study, a box containing ASCEND tablets (and also a consent form) will be mailed to you. A copy of this consent form will also be mailed.

If the questionnaire suggests that you are not eligible to take part, you will be told so.

Thank you very much.

Dr Deepak Bhatnagar
Consultant/Senior Lecturer in Diabetes & Metabolism
Royal Oldham Hospital

Dr Biswa Mishra
Consultant Diabetologist and Endocrinologist
Royal Oldham Hospital

Mr Thomas White
24 Raspberry Road
Gardentown
Gerrards Park
DB3 STR

Dear Mr White,

ASCEND: A Study of Cardiovascular Events in Diabetes

We are writing to invite you to participate in the ASCEND research study of the prevention of heart attacks and strokes in people with diabetes. At the Diabetes Centre at The Royal Oldham Hospital, we are working with Oxford University’s Clinical Trials Service Unit to help identify suitable people for this nationwide study. So, we are writing (having first informed your GP, Dr Rosal Gardner) to all those people on our local diabetes register who are aged over 40 and likely to be suitable, in order to find out whether they might be interested in taking part. The purpose of the study is to assess whether aspirin and/or naturally-occurring olive oil are useful for preventing heart attacks and strokes in people with diabetes who have not had circulatory problems.

Please read the enclosed Information Leaflet entitled “ASCEND: Invitation to join a large medical research project”, It is then up to you whether or not you would like to take part. If you would like to, then please complete the attached questionnaire. Follow all instructions in the questionnaire and sign the Agreement to Participate. We want you to take part and to complete the questionnaire and sign the Agreement to Participate. We hope you will decide to take part in ASCEND.

If you do not want to participate then please indicate this on the questionnaire on the back of this letter so that you do not get approached again. In either case, please return the questionnaire in the Freepost envelope provided.
Pre-randomisation run-in phase

- GP informed that patient has entered run-in; option to withdraw
- Blood kit mailed during run-in period
- Randomisation form mailed after 6 weeks
Baseline blood samples (optional)

- 22,900 blood and urine kits sent out
- 13,000 participants returned samples
- 11,500 from randomised participants (74%)
- HbA1C, TC, HDL c, Apo A1, Apo B, urinary albumin/creatinine measured on fresh samples
- Urine, plasma, red cells and genetic material stored long-term
ASCEND Document Ref. A796-0673

Mr Maurice Stigwood
13 Hopkins Road
Hogford
Hogwoodshire
HG5 8PG

28 November 2006

Dear Mr Stigwood,

ASCEND: A Study of Cardiovascular Events in Diabetes

It is now about 2 months since you provisionally agreed to take part in ASCEND and received a box of study treatment. We would now like to know whether you are happy to continue into the long-term part of the ASCEND study. You may remember that the purpose of the study is to assess whether aspirin and/or naturally-occurring oils are useful for preventing heart attacks and strokes in people with diabetes who have not already had diagnosed circulatory problems.

On the back of this letter is a brief questionnaire which we would like you to complete and sign. Then please return it in the enclosed Freepost envelope. If you have any questions regarding the study you may telephone us or one of the other ASCEND staff on Freefone 0800 585323. Alternatively, you may wish to discuss matters with your GP or diabetes nurse before deciding whether to continue.

We hope you will decide to continue in ASCEND. If you do, then we shall send a new pack of study treatment as soon as we have received this completed form back from you. Subsequently, you will be sent a brief questionnaire to complete every six months and new supplies of study treatment. Alternatively, if you do not want to participate then please indicate this on the form and return it in the Freepost envelope provided.

Yours sincerely

[Signatures: Jane Armitage, Study Coordinators; Dr. Louise Bowman]

On behalf of Dr John Smith, Hogford General Hospitals NHS Trust

Enc. FREEPOST envelope

Thank you very much
ASCEND: Randomisation Questionnaire

INSTRUCTIONS FOR COMPLETION
Please complete the questionnaire in BLOCK CAPITALS using blue or black ink.
Please place a cross in the appropriate box, e.g. Yes ☑ No ☐
(if you make a mistake, fill the entire box and mark the correct box, e.g. Yes ☑ No ☐)
OR write clearly in the appropriate boxes, e.g. 26 01 2007

1. Contact and GP Details
Please check that the contact details for you and your GP are correct. If not, then please call Freefone 0800 585323 and provide the correct information. Please quote the reference number from the covering letter on the front of this questionnaire.
Your details:
Mr Maurice Stratwood
13 Hogben Road
Hogford
Hogwoodshire
HG2 8PG
09453 33993 (day); 09453 33993 (home)

2. Continuing in ASCEND
Are you willing to continue taking study tablets and capsules in ASCEND for the next 5 years? Yes ☑ No ☐
If you answered YES, then please complete ALL the remaining sections of this questionnaire, sign and date the form, and return it in the FREEPOST envelope provided.
If you answered NO, then return the questionnaire in the FREEPOST envelope provided (but do not complete the remaining sections).

3. About Your ASCEND Medication
Please indicate how regularly you have taken your ASCEND medication since you received it:
White Tablets Brown Capsules
Every day ☐ Some days ☐ Only occasionally ☐ Never ☐
Most days ☐ Please cross ONE box only in EACH column

4. About Your Diabetes
4.1 What year was your diabetes diagnosed? ☐
4.2 Do you inject INSULIN for your diabetes? Yes ☑ No ☐
4.3 If Yes, did you start insulin within one year of having diabetes? Yes ☑ No ☐
4.4 Are you known to have diabetes changes at the back of the eye? Yes ☑ No ☐
4.5 If Yes, have you ever had laser treatment to the eye for this? Yes ☑ No ☐
4.6 Do you take treatment for high blood pressure or hypertension? Yes ☑ No ☐

5. Confirming Your Medical History
5.1 Has a doctor ever told you that you had any of the following?
   a) Heart attack ☐ Yes ☑ No ☐
   b) Angina (chest pain from the heart) ☐ Yes ☑ No ☐
   c) Stroke or minirstoke (sometimes called TIA) ☐ Yes ☑ No ☐
   d) Coronary artery bypass operation (CABG or "cabbage") ☐ Yes ☑ No ☐
   e) Coronary angioplasty ("balloon", "stent" insertion or PTCA) ☐ Yes ☑ No ☐
   f) Other arterial surgery or angioplasty (e.g. leg bypass) (Do not include angiogram)
      If Yes, please specify:
   g) Liver disease (active or chronic, or cirrhosis) ☐ Yes ☑ No ☐
      If Yes, please specify:
   h) Cancer within the last 5 years (e.g. skin, breast, lung, bowel etc) Yes ☑ No ☐
      If Yes, please give the type of cancer:
   i) Other serious illness ☐ Yes ☑ No ☐
      If Yes, please specify:

5.2 In the last 6 months have you been in hospital with, or has a doctor said you have:
   a) Active peptic (stomach or duodenal) ulcer? Yes ☑ No ☐
   b) Bleeding from the stomach or bowel? Yes ☑ No ☐
   c) Inflamed bowel? Yes ☑ No ☐
   d) Ulcerative colitis? Yes ☑ No ☐
   e) Inflammatory bowel disease (Crohn's)? Yes ☑ No ☐
   f) Other serious illness ☐ Yes ☑ No ☐
      If Yes, please specify:

6. About You
6.1 Please give your date of birth: ☐
   Day ☐ Month ☐ Year ☐
6.2 Which best describes your ethnic origin?
   White ☐ Black: African/Caribbean ☐
   Indian, Pakistani or Bangladeshi ☐ Other ☐
   Please cross ONE box only
6.3 Please provide your weight in light indoor clothes without shoes (round to nearest whole number):
   kgs ☐ stones ☐ lbs ☐
6.4 Please provide your standing height without shoes (round to nearest whole number):
   cms ☐ feet ☐ inches ☐
6.5 Do you smoke cigarettes regularly (i.e. on most days)? Yes ☑ No ☐
   If Yes, give approximate number smoked per day:
6.6 If No, have you ever smoked regularly? Yes ☑ No ☐
   If Yes, give the age you stopped:
   years ☐

ASCHEN Pre-Intervention Questionnaire 2 of 3 5/8/2007

Need help completing this form? Please call Freefone 0800 585323
ASCEND: recruitment completed July 2011

<table>
<thead>
<tr>
<th></th>
<th>Centrally-held Register</th>
<th>GP practices</th>
<th>Others *</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitations sent</td>
<td>300,188</td>
<td>120,875</td>
<td>2223</td>
<td>423,286</td>
</tr>
<tr>
<td>Patients enter Run-in</td>
<td>16,104</td>
<td>9,741</td>
<td>635</td>
<td>26,480</td>
</tr>
<tr>
<td>Patients randomised</td>
<td>9013</td>
<td>6037</td>
<td>430</td>
<td>15,480</td>
</tr>
<tr>
<td></td>
<td>(3.0%)</td>
<td>(5.0%)</td>
<td>(19%)</td>
<td>(3.7%)</td>
</tr>
</tbody>
</table>

* HPS follow up/Self/friends/Hospital referral
Follow-up by mail

- Follow-up questionnaires sent 6 monthly:
  - serious adverse events
  - significant bleeding episodes
  - study treatment compliance
  - non-study treatments of interest
- Treatment packs mailed at appropriate intervals
- Central registries (death, cancer, MI, cardiac interventions, hospital admissions)
- 24 hour freephone telephone service
**ASCEND: Follow-up Questionnaire**

**Instructions for Completion:**
Please complete the questionnaire in BLOCK CAPITALS using blue or black ink. Please place a cross in the appropriate box, e.g. Yes [X] No [ ] (if you make a mistake, fill the entire box and mark the correct box, e.g. Yes [X] No [ ].)

**1. Contact and GP Details**
Please check that these contact details are still correct. If not, then please telephone 0800 585323 and provide the correct information. Please quote the reference number from the covering letter on the front of this questionnaire.

**Your details:**
Alternative contact: GP details:
Mr Thomas White
24 Raspberry Road
Gardentown
Gardenshire
GA3 5TR
01234 567890

**2. ASCEND Medication**
2.1. Please indicate how regularly you have taken your ASCEND medication during the last 6 months:

<table>
<thead>
<tr>
<th>White Tablets (aspirin/placebo)</th>
<th>Brown Capsules (one or other natural oil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every day</td>
<td>[ ]</td>
</tr>
<tr>
<td>Most days</td>
<td>[ ]</td>
</tr>
<tr>
<td>Only occasionally</td>
<td>[ ]</td>
</tr>
<tr>
<td>Never</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

2.2. Are you willing to continue taking the white (aspirin/placebo) ASCEND tablets?

Yes [ ] No [ X ]
If No, please tell us why:

2.3. Are you willing to continue taking the brown (one or other natural oil) ASCEND capsules?

Yes [ ] No [ X ]
If No, please tell us why:

**3. Other Current Medication**
3.1. Do you currently take any of the following regularly (i.e. more than one day per week)?

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes [ ]</th>
<th>No [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Warfarin (Marvaran), Aenocoumarol (Nicoumalone, Synthrom) or Phenindione</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>b) Aspirin, prescribed or over-the-counter (e.g. Aradin, Caprin, Disprin, Imazo PostMi). Do not include your ASCEND study tablets</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>c) Clopidogrel (Plavix)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>d) Dipryidamole (Persantin, Persantin Retard or Assalasin Retard)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**4. Medical Events**
4.1. Since completing your last questionnaire on [date] have you had ANY of the following? (If Yes, please give the date and the name and town of the hospital you attended). Please note there is extra space overlaid to list second occurrences of any of the medical events listed below:

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Yes [ ]</th>
<th>No [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Heart attack</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>b) Admission to hospital with angina or any chest pain</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>c) Stroke</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>d) Ministroke (sometimes called TIA)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>e) Coronary artery bypass operation (CABO or “cabbage”)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>f) Coronary angioplasty (“balloon”, “stent” insertion or PTCA)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>g) Other arterial surgery or angioplasty (e.g. leg bypass)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>h) Cancer (e.g. skin, breast, lung, bowel etc)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>i) Bleeding for which you saw a doctor (e.g. serious nose bleed, bleeding in the eye)</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>j) Site in body of bleeding</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>k) Were you admitted to hospital?</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>l) Name and town of hospital attended</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
ASCEND Document Ref. A777-7772

Mr Thomas White
24 Raspberry Road
Gardentown
Gardenshire
GAS STR

Dear Mr White:

ASCEND: A Study of Cardiovascular Events in Diabetes

Thank you for your continued participation in ASCEND and your commitment to research into diabetes. On the back of this letter is a simple questionnaire similar to earlier ones you have returned. We would be grateful if you would complete and return it promptly in the Freepost envelope enclosed. We cannot emphasise enough how important it is that we receive this information regularly from each of the participants in ASCEND. We shall be sending you a new supply of study treatment automatically when it is required.

Please let us know if you have any questions or need help completing the questionnaire, by telephoning Freephone: 0800 585323.

Thank you for your continued support of ASCEND, and for being prepared to complete regular questionnaires. We are grateful for your help with finding ways of preventing the complications of diabetes.

Yours sincerely,

Dr Jane Armitage

Dr Louise Bowman

Study Coordinators

On behalf of [local collaborator]

Thank you for your continued participation in ASCEND
Welcome to the eighth edition of Himalaya – the newsletter of the ASCEND study. Thank you very much for your interest and participation in the ASCEND study so far. If you have not received Himalaya before, we hope this newsletter will educate and entertain you, and tell you more about the study that you are playing such a vital role in. If you have, then read on and find out what we have been up to since the last issue.

WE HAVE REACHED 12,000 PARTICIPANTS!

People from all over the UK are participating in ASCEND. We collect data on everyone who participates and here are some of the characteristics of the people taking part:

- 62% are men and 38% are women;
- 93% of people have type 2 diabetes;
- average age is about 62 years;
- participants have had diabetes for an average of 10 years before entering the study;
- about 1 in 3 participants take insulin.

HOW DO I GET THE TABLETS OUT OF THE PACKS?

We know some of you have difficulty getting the study treatments out of the packaging. The packaging technology is currently under review due to the problems encountered and we will let you know if there are any changes.

ASPIRIN AND CANCER

You might have read or heard the recent news stories about the effect of aspirin on cancer. This is indeed an interesting news, but as yet the answer is not clear. The relative benefits of aspirin on cancer are not known. If you are taking aspirin, it is well to know that the risk of bleeding is increased with long-term aspirin use. In particular, the recent publications have focused on the risk of bleeding rather than the benefits on cancer. It is important to note that there is no evidence that aspirin reduces the risk of cancer in people who already have a cancer. We do not know if aspirin is effective in preventing cancer. We do not know if aspirin is effective in preventing cancer.

THE ASCEND TEAM

THE ASCEND TEAM

The three people in the picture (left to right) are the ASCEND team. They have been responsible for answering many questions and dealing with patients. They have been responsible for answering many questions and dealing with patients.

WHERE CAN PEOPLE FIND OUT MORE?

They can:

- visit the ASCEND website: www.ctsu.ox.ac.uk/ascend
- call a member of the study team: (Freephone) 0800 585523
- www.ctsu.ox.ac.uk/ascend

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Summary of experience in ASCEND

- Successful recruitment of 15000 trial participants by mail using centrally-held and GP databases
- Streamlined trial design, simple CRFs completed by participants – no study clinics
- Follow-up is on-going, results anticipated 2017
- Results relevant to 350 million people worldwide with diabetes
The evolution of diabetes