ASCEND (A Study of Cardiovascular Events iN Diabetes):

A randomised 2x2 factorial design study of aspirin versus placebo, and of omega-3 fatty acid supplementation versus placebo, for the primary prevention of cardiovascular events in people with diabetes

Should aspirin be used routinely in people with diabetes but no vascular disease?

The role of antiplatelet therapy (chiefly aspirin) for the *secondary* prevention of cardiovascular disease is firmly established for many high-risk groups with diagnosed occlusive arterial disease, and the proportional reductions in heart attacks and strokes appear to be similar whether or not these patients have diabetes. But, most younger and middle-aged people with diabetes do not have manifest arterial disease – although they are still at significant cardiovascular risk – and yet the available randomised evidence for the use of antiplatelet therapy in such individuals is sparse. As a result, there is major uncertainty about the role of antiplatelet therapy for the *primary* prevention of cardiovascular events among people with diabetes, and only a small minority receives it.

ASCEND aims to demonstrate whether aspirin reduces the risk of cardiovascular events in individuals with diabetes who do not already have diagnosed occlusive arterial disease, and whether such benefits outweigh any potential hazards from bleeding. In order to do this reliably, at least 10,000 patients with diabetes and no clinical evidence of occlusive arterial disease will be randomly allocated to receive 100mg aspirin daily or matching placebo tablets for about 5 years. A study of this size should have excellent power to detect a 20% proportional reduction in the cardiovascular event rate among such patients.

Do omega-3 fatty acids (fish oils) reduce cardiovascular risk in people with diabetes?

There is consistent evidence from observational studies of lower rates of cardiovascular disease (particularly cardiac and sudden death) in people with higher intakes, or higher blood levels, of omega-3 fatty acids (FA). Randomised evidence among people who have survived a heart attack suggests modest, but potentially worthwhile, reductions in coronary events of 15-20%. There is, however, no large-scale randomised evidence for the use of omega-3 fatty acids in the primary prevention of vascular events. People with diabetes are at increased cardiovascular risk, and may gain particular benefit from the effects of omega-3 fatty acid supplementation on platelet aggregation and dyslipidaemia. Hence, participants in ASCEND will also be randomly allocated in a 2x2 factorial design to receive 1g omega-3 FA daily or matching placebo capsules for about 5 years. Such a study design allows all randomised patients to contribute fully to the assessment of the separate effects of aspirin therapy and of omega-3 fatty acids.

ASCEND: A streamlined, mail-based trial collecting only essential data

The reliable assessment of the important questions that ASCEND is addressing requires the randomisation of a very large number of people with diabetes, and their long-term treatment and follow-up. In order to be able to study 10,000 people with diabetes for about 5 years at low cost, ASCEND is streamlined and being undertaken predominantly by mail (supplemented by central records). If it can reliably demonstrate that aspirin and/or omega-3 fatty acids safely reduces the risk of cardiovascular events and deaths in patients with diabetes who do not have pre-existing occlusive arterial disease, then this would be relevant to some tens of millions of people world-wide (who are currently not receiving such therapy) and could save tens of thousands of lives each year. Consequently the British Heart Foundation is supporting this large streamlined trial.

ASCEND: SUMMARY OF PRACTICAL PROCEDURES

POTENTIALLY ELIGIBLE

- Diabetes mellitus (type 1 or 2)
- Male or female
- No diagnosed occlusive arterial disease
- Aged ≥ 40 years

IDENTIFICATION & INVITATION

- Potentially eligible patients identified from existing diabetes registers or databases and other sources
- Invited by GP, diabetologist or study coordinators, either in person or by mail. Invitation includes Information Leaflet, Consent Form and brief Screening Questionnaire
- Central Freefone number for any questions

SCREENING PROCESS (-2 months)

- Screening Questionnaire returned, which identifies eligible and consenting patients
- Run-in pack with 2-month supply of placebo treatment mailed to patient
- GP informed of patient's possible participation, and asked to return form if patient **not** to be randomised
- Blood and urine samples (optional) collected locally and mailed to central laboratory
- Freefone number (0800 585323) for medical advice and any questions

RANDOMISATION (0 months)

- Randomisation Questionnaire sent to re-confirm eligibility, and to characterize the patient more fully
- Randomisation Questionnaire returned, and eligible patient randomised by central computer
- Allocated treatment pack mailed to patient: 100 mg aspirin daily or matching placebo tablet, and 1g omega-3 FA daily or matching placebo capsule
- GP informed of patient's randomisation

FOLLOW-UP QUESTIONNAIRES (6-monthly)

- Follow-up Questionnaires and treatment packs sent 6-monthly
- Freefone number (0800 585323) for medical advice and any questions
- Further details sought from responsible clinicians about any relevant events reported on Follow-up questionnaires
- Flagging for mortality and cancer at central registries