HEAT - Helicobacter eradication to prevent ulcer bleeding in aspirin users: a large simple randomised controlled trial

Peptic ulcer is a serious cause of death in the UK. A serious complication of this illness is ulcer bleeding, and previous research has established that aspirin use increases the risk of bleeding.

Approximately 28% of people aged 60 years and over in England take aspirin, and there has been a huge increase in aspirin use over the past 10 years. People who suffer peptic ulcers and are taking aspirin are often given Protein Pump Inhibitors (PPIs) to reduce the risk of internal bleeding.

However PPIs come at a significant medical cost, e.g. increased risks of *C. difficile* infection and interaction with the drug clopidogrel. An alternative strategy for reducing the life-threatening risks of ulcer bleeding is to eradicate the levels of *Helicobacter pylori* in patients' bodies. *H. pylori* is a bacteria that lives in the stomach, and is found naturally in around half of the world's population. In most people *H. pylori* does not cause any illness, but it does increase the chance of developing stomach ulcers. *H. pylori* eradication is likely to be highly cost effective because a single intervention would reduce subsequent hazards on a continuing lifelong basis. The trial itself is likely to be a cost effective therapeutic intervention: it is estimated that it will prevent 585 hospitalisations and 59 deaths from stomach ulcer bleeding, saving approximately £5.85 million.

A valuable component of the trial will be an economic assessment of the monetary value of the proposed treatment. This will be extended beyond direct costs of hospitalisation to include the costs of avoidable events and mortality associated with *H. pylori*, avoidable events and mortality associated with non-use of aspirin, and avoidable post-bleed complications and alternative treatment with PPIs. The trial will also examine potential benefits of a possible expansion in aspirin use that a positive result might stimulate.

Open all sections

Design

Double-blind, placebo-controlled randomised multi-centre study of the effects of *H. pylori* eradication treatment on subsequent ulcer bleeding in infected individuals taking aspirin ≤325mg daily. The trial will use methods validated during the pilot study.

Participants will be randomised to receive active or placebo *H. pylori* eradication treatment. Active treatment will consist of seven days of lansoprazole 30mg twice daily, clarithromycin 500mg twice daily and metronidazole 400mg twice daily. Placebo will be manufactured to match the active drug. Participants will continue to take aspirin at their prescribed dose.

An important component of this study is the attempt to develop low-cost, streamlined, simplified methodologies to bring outcome studies within the capability of academic investigators. New MHRA guidelines from 1 April 2011 are helpful to this aspiration. This guidance suggests that this is a Type A trial because it only uses established medical products given for their licensed indications and "no higher than the risk of standard medical care".

Aim of study

Use of aspirin for cardiovascular prophylaxis (and potentially cancer prevention) is widespread and increasing. The main hazard is ulcer bleeding. This is usually associated with *H. pylori* infection. It is important to determine whether this can be reduced or prevented by *H. pylori* eradication. Given the scale of aspirin use, its continuing increase and its contribution to ulcer bleeding, how to deal with this problem is arguably the most important question with regard to current iatrogenic medicine.

The research has three primary objectives:

1. Medical: To test the hypothesis that a one-week course of *H. pylori* eradication in patients using aspirin ≤325mg daily will reduce the incidence of subsequent adjudicated peptic ulcer bleeding that results in hospitalisation.

2. Economic: To test the hypothesis that the intervention has a positive net monetary benefit.

3. Methodological: To establish a methodology for large simple outcomes studies using electronically extracted Primary Care follow-up data, to reduce costs to a level that enables outcomes studies of clinically important questions to be done without the need for industry support.

Secondary medical objectives include evaluating the effect of *H. pylori* eradication on other GI and cardiovascular outcomes.

Setting

Patients will be recruited from Primary Care practices. There will be four trial centres: Nottingham, Durham, Birmingham/Oxford and Southampton, and the trial will recruit across these regions.

Target population

Males and females 60 years of age or older, who are taking aspirin at a dose of 325mg per day or lower, and who have had 4 or more 28-day prescriptions in the past year.