Helicobacter pylori eradication for primary prevention of peptic ulcer bleeding in older patients prescribed aspirin (HEAT): a randomised placebo-controlled trial in primary care.

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ABSTRACT

Background:

Peptic ulcers in patients on aspirin are associated with *Helicobacter pylori* infection. We investigated whether *H. pylori* eradication would protect against aspirin associated ulcer bleeding

Methods:

The *Helicobacter* Eradication Aspirin Trial (HEAT) was a randomised placebo-controlled trial (EudraCT 2011-003425-96), conducted in UK primary care using routinely collected clinical data. Consenting patients aged ≥60 years prescribed aspirin ≤ 325 mg but not ulcerogenic or gastroprotective medication underwent C13 urea breath testing for *H. pylori*. Those with a positive test were randomised to receive either a combination of clarithromycin 500mg, metronidazole 400 mg and lansoprazole 30mg, or placebos twice daily for seven days . Follow up was by scrutiny of electronic data in primary and secondary care. The primary outcome, time to hospitalisation due to definite or probable peptic ulcer bleeding, was analysed by Cox proportional hazards methods

Findings:

Between 14 September 2012 and 22 November 2017, 30,166 patients underwent breath testing, 5367 had a positive result, 5352 were randomised to an ITT population of 2677 (eradication) and 2675 (placebo) and followed up for median 5 years. Statistical analysis of the primary outcome showed a significant departure from proportional hazards assumptions (p=0.0068), requiring analysis over separate time periods. There was a significant reduction in the primary outcome in the eradication arm in the first 2.5 years (hazard ratio 0.35 (95% CI 0.14 to 0.89, p= 0.028) with 6 episodes, (rate 0.92 [95% CI 0.41 to 2.04])/1000 person years) vs control: 17 episodes, (rate 2.61 [95% CI 1.62 to 4.19]/1000 person years) attributable to reduced gastric and duodenal ulcer bleeding. This advantage remained significant when adjusted for the competing risk of death (p = 0.028) but was lost with longer follow up (HR 1.31, 0.55 to 3.11)

Interpretation:

H. pylori eradication protects against aspirin associated peptic ulcer bleeding, but this may not be sustained.

299 words

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Introduction

Aspirin is widely recommended for the secondary prevention of thrombotic vascular disease[1-5]. Its use is limited principally by increased bleeding particularly from the gastrointestinal tract[7,8]. Whether there is net benefit from aspirin in primary prevention is currently the subject of debate[4,5]. The risks of upper gastrointestinal (UGI) bleeding can be mitigated in part by acid suppression with proton pump inhibitors (PPIs) and probably Histamine H2 receptor antagonists (H2RA)[8-10]. However, although anti-inflammatory doses of aspirin are intrinsically ulcerogenic, the much lower doses used for prevention of thrombosis are less damaging[11]. There is evidence that *Helicobacter pylori* may play a central role in development of peptic ulceration[12-15] and ulcer bleeding[16-18] in these patients but these data are largely observational and do not establish a causal role.

These studies suggest eradication of *H. pylori* as a therapeutic target but randomised controlled trials have been limited to secondary prevention of recurrent ulcer bleeding and have yielded discordant results[19,20]. One trial of 250 participants reported a six month incidence of ulcer rebleeding following *H. pylori* eradication (1.9%) not significantly different from that with PPI co-prescription (0.9%)[19] whilst another trial of 123 participants reported 12 month rebleeding rates significantly greater than those with PPI co-prescription (14.8 % vs 1.6%)[20]. The American College of Gastroenterology guidelines suggest testing for *H. pylori* when starting prophylactic low-dose aspirin, while acknowledging that the evidence base for this recommendation is weak, observational, and based on indirect extrapolation. In view of these uncertainties, we conducted a large randomised controlled trial of *H. pylori* eradication for the prevention of ulcer bleeding in patients aged $\geq$ 60 who were prescribed aspirin.

Methods

Design

The *Helicobacter* Eradication Aspirin Trial (HEAT) was a double-blind randomised placebo-controlled trial (EudraCT number 2011-003425-96) that investigated the hypothesis that a 7-day course of *H. pylori* eradication therapy would reduce the incidence of subsequent peptic ulcer bleeding in infected patients. The study was sponsored by the University of Nottingham and funded by the Health Technology Assessment programme of the UK's National Institute for Health Research (NIHR). It was undertaken in accordance with International Conference on Harmonization guidelines and the Declaration of Helsinki and was approved by East Midlands – Leicester Central Research Ethics Committee (REC 11/EM/0434)

HEAT was conducted using novel real-world methodology developed by the Simple Trials for Academic Research (STAR) group in Nottingham. Following pilot funding from the Medical Research Council a network of collaborating general practitioner (GP) investigators was developed[22,23]. The trial was coordinated from four UK research centres: Nottingham, Birmingham/Oxford, Durham, and Southampton. Participating GP investigators used a bespoke digital tool to screen for patients meeting eligibility criteria and contacted them via a highly secure automated online mail management system[24] to invite trial participation. To maintain data security, the patient's NHS number was encrypted (using the AES-256 encryption standard), with the NHS number itself as the unique encryption key to allow decryption. Interested patients contacted the trial team who arranged an in-person screening visit hosted by HEAT specific or generic NIHR research nurses at their general practice to check suitability, obtain consent and carry out an *H. pylori* breath test (Supplementary Information).

Participants

Men and women age $\geq$ 60 years, who were taking aspirin $\leq$325mg daily and who had had four or more 28-day prescriptions for aspirin in the past year were eligible for enrolment if they had a positive *H. pylori* C13 urea breath test at the screening visit. Ongoing additional use of other anti-platelet agents was allowed. Patients who were on non-steroidal anti-inflammatory drugs (NSAIDs) or gastroprotective drugs at their baseline screening visit were excluded from participation, but these drugs could be started during follow up if clinically indicated. Patients with allergy or intolerance to *H. pylori* eradication treatment or who needed to continue taking drugs with a clinically

significant interaction with *H. pylori* eradication treatment were excluded from the trial (Supplementary Information Table S1).

H. pylori status was determined using the Helicobacter Test INFAI[25], conducted by trained research nurses during the patient's screening visit (Supplementary Information). Samples were posted to INFAI and analysed via a dedicated workstream. Patients with a negative or borderline *H. pylori* breath test were not eligible for the trial but these patients and their GPs were informed of their result.

Randomisation and masking

Patients meeting eligibility criteria who had an unequivocally positive breath test were randomly assigned to receive active *H. pylori* eradication treatment or placebos on a 1:1 basis. Randomisation was carried out by Nottingham Clinical Trials Unit using a validated, web-based system with separate sequences for each regional centre using permuted blocks of randomly varying size.. The participants, their GPs and health care providers, the research nurses, trial team, Adjudication Committee and analysis team were all blinded throughout the trial to the treatment allocation until after the analysis was complete. The Nottingham Clinical Trials unit retained the key to unmask the data throughout the trial. Individual unmasked data could be supplied to the trial pharmacist for safety reasons.

Interventions

Active treatment consisted of twice daily lansoprazole 30mg, clarithromycin 500mg and metronidazole 400mg, taken for one week[26]. Control patients received placebos corresponding to each of the active treatments to be taken twice daily for one week. Active and placebo treatments (Supplementary Information) were stored and dispensed from a dedicated pharmacy unit maintained by the coordinating centre in Nottingham and were posted to patients upon receipt of a positive breath test result, together with a returnable report form recording the date of receipt, timing of doses taken and any adverse events.

Patients made no more trial visits after screening but were contacted annually to prompt reporting of any events. They remained under trial follow up until the end of the trial (June 30, 2020) or until they died (from any cause) or withdrew permission for further use of their data. Those who asked to disengage from annual contact remained part of the trial database. Patients who moved to a different general practice remained in trial follow up. A randomly selected 10% sample of participants were sent a repeat *H. pylori* breath test between February 5th and September 6th 2019 to be done at home[27] to assess the antibacterial efficacy of the eradication treatment.

Events during follow-up were identified from searches of Hospital Episode Statistics (HES), Office of National Statistics (ONS) mortality data, GP databases using MIQUEST software[27,28], and from patient and GP spontaneous reports. For patients who moved to practices not participating in HEAT, follow up information was available using nationally held HES and ONS data but these patients were censored at the date of moving practice for outcomes that relied on primary care data. All plausible episodes which mentioned GI bleeding or peptic ulcer in any of these data sources were evaluated by a blinded adjudication committee comprising three specialist clinicians (Supplementary Information). A complete listing of data from HES, supplied annually, covered the period from trial start (September 14, 2012) to finish (June 30, 2020). Primary care data were uploaded from individual practices intermittently. GPs were asked to do an end of study upload, but this was not always possible in part because of disruption by the Covid pandemic: data from those practices used to determine secondary outcomes using primary care data were censored from the date of their last upload.

Outcomes

The primary endpoint was the first episode of hospitalisation or death due to definite or probable peptic ulcer bleeding, as determined by the adjudication committee, guided by the criteria of the TARGET study. These use the clinical presentation, its severity, and the endoscopic findings to generate a series of likelihood scenarios[29] (Details in Supplementary Information). Secondary endpoints included time to first episode of hospitalisation or death due to gastric or duodenal ulcer bleeding (oesophageal ulcer bleeds excluded), all other causes of clinically significant GI bleeding, thrombotic cardiovascular outcomes, detected uncomplicated ulcers, number of GP consultations for dyspepsia and time to first prescription for PPI medication or other anti-ulcer/dyspepsia medication (H2 receptor antagonist, antacid, alginate). Uncomplicated ulcers were those detected in the absence of clinically significant bleeding. Cardiovascular events were based on unadjudicated ICD10 codes recorded in HES or ONS for myocardial infarction (MI), cerebrovascular accident (CVA) and sudden cardiac deaths (Supplementary information).

Adverse events (AEs) and death

Because patients only received 1 week of already well characterised treatment, and in conjunction with MHRA, we set a four-week window for the routine collection of suspected treatment-related adverse events reported by patients on the report form sent in each treatment pack. Serious AEs reported by GPs outside this window were also collected as well as all deaths recorded by ONS.

Statistical analysis

An intention to treat (ITT) analysis was carried out including all randomised patients irrespective of whether they took the treatment, or the number of doses taken but excluding one patient who died and three patients who experienced ulcer bleeding between the screening visit and the randomisation date and one patient not properly consented. Kaplan Meier survival curves were plotted for time to first event outcomes, censoring at the date of first event, death, trial withdrawal or study end date.

A Cox proportional hazards model, adjusted for regional centre as a fixed effect, was used to calculate hazard ratios (HR) and 95% confidence intervals comparing treatment arms for the primary endpoint. The assumption of proportional hazards was examined by a Schoenfeld test based on scaled Schoenfeld residuals and assessed graphically by a log minus log plot[30]. Where there was clear evidence of violation of the proportional hazards assumption, hazard ratios were calculated for separate periods of follow up split at the median time to event after randomisation. The number needed to treat (NNT) to avoid one ulcer bleed was calculated using the time to event method of Altman et al[31]

Sensitivity analyses assessed the effect of adjusting for age and sex and including ulcerogenic and gastroprotective drugs as time varying exposures in the model. . A between treatment arm and age interaction was assessed for significance using a likelihood ratio. A Fine-Gray model was used to estimate the subdistribution HR for the association of eradication and the primary outcome accounting for the competing risk of death[32]. A per protocol analysis was carried out restricted to patients who reported that they had taken eight or more doses of trial medication.

The time to event secondary outcomes were analysed using Cox proportional hazard models. The numbers of GP-recorded dyspepsia consultations during follow-up were compared between treatment arms using negative binomial regression to calculate rate ratios and 95% confidence intervals accounting for overdispersion. Time to first prescription for PPI medication or other antiulcer/dyspepsia medication (H2 receptor antagonist, antacid, alginate) during follow-up were compared between treatment arms using Cox proportional hazards models. The point prevalence of prescriptions for aspirin, PPIs and H2 receptor antagonists were estimated at 6 monthly time points throughout the study follow-up period.

HEAT was intended to be event driven. Based on published data we assumed an ulcer bleeding rate of 8 per 1000 patient years in the control arm[22]. To detect a hazard ratio of 0.5 comparing the intervention with the control arm, with a 5% two-sided significance level and 90% power a total of 87 events would be required, , with 145,000 person years of exposure. Due to a shortfall in both the anticipated proportion of patients that were *H. pylori* positive and in the primary endpoint rate, recruitment and follow up periods were lengthened. Due to concern that competing risks (including death) would become the dominant influence with an excessively long follow up period, the trial was stopped when 44 primary endpoints had occurred.

Funding:

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Results:

The trial was conducted in 1,208 GP practices across the whole of the UK (approximately 13% of the total number of GP practices), predominantly in England and Wales. Between 14 September 2012 and 22 November 2017 participating GPs sent 188,875 invitation letters; 30,166 patients (16.0%) gave consent to trial participation, of whom 5367 (17.8%) had a positive *H. pylori* breath test, and 5357 were randomised (between 1 and 33 patients from each of 1055 practices), with 5352 patients in the ITT population (Figure 1).

Mean age at consent was 73.6 (SD 6.9) years and 72.8% of participants were male. Treatment arms were well balanced for ulcer risk factors and demographic features (Table 1). Coronary heart disease was the most common co-morbidity among aspirin indications, followed by diabetes mellitus and a history of stroke or transient ischaemic attack (Table 2). Ten percent of patients were prescribed nitrates. Fewer than 2% had a history of peptic ulcer. Use of drugs capable of influencing ulcer development prescribed in the 90 days prior to the date of randomisation are shown in Table 2. In the 10% retest sample of patients at a median of 3.95 (IQR

2.76, 5.28) years after randomisation, 146 in the eradication arm (90.7%) had a negative breath test vs 41 (24.0%) in controls (p<0.001).

Randomised patients were followed up for a total of 26,668 person years (median 5.0 years IQR 3.9 to 6.4) until they withdrew consent, died, or reached the end of the study (June 30, 2020). During this time there were 141 episodes of clinically significant GI bleeding: 44 patients had first episodes which were adjudicated as definite or probable peptic ulcer bleeds, 18 in the active eradication arm and 26 in controls (Table 3)

Figure 2 shows Kaplan Meier survival curves for the primary outcome, with early separation between the treatment arms. A Schoenfeld test showed a significant departure from the Cox proportional hazards assumption (p=0.0068). This was due to a marked difference between the treatment arms early in the study, but not later (Figure 2, and Supplementary Figure S2). Accordingly we fitted one Cox model with time split in the data at the median of 2.5 years, because this resulted in similar numbers in the first and second period, which minimised loss of statistical power. This resulted in the Cox proportional hazards assumptions being met (p=0.54 for the overall model). There were 23 episodes of ulcer bleeding adjudicated as a primary outcome in the first 2.5 years, 6 in the active eradication arm and 17 in controls and 21 after 2.5 years, 12 in the active eradication arm and 9 in controls. The hazard ratio (HR) in the first 2.5 years was 0.35 (0.14 to 0.89, p= 0.028, Table 3), with a rate of 0.92 [0.41 to 2.04]/ 1000 person years in the eradication treatment arm and 2.61 [95% CI 1.62 to 4.19]/ 1000 person years in the control arm and an NNT of 238 (95%CI 184 to 1661). In the period after 2.5 years there were 9 episodes in the control arm (rate 1.33 [0.69 to 2.56] /1000 person years) and 12 in the eradication treatment arm (rate 1.75 [0.99 to 3.08] / 1000 person years, with an HR of 1.31 [0.55 to 3.11], p = 0.540, Table 3). Results were similar after adjustment for age and sex (Table 3). There was no significant interaction with age, although the low number of events limited our power for subgroup analyses.

A Fine-Gray model used to adjust for the competing risk of death showed the difference between the eradication arm and control arm remained significant in the first 2.5 years (subdistribution HR within 2.5 years 0.35 [0.14-0.89], p = 0.028, Supplementary Table S2 and Figure S3). In the per protocol analysis of the 4369 patients who had taken at least 8 eradication doses, there were 34 peptic ulcer bleeds adjudicated as primary outcomes, with 18 occurring in the first 2.5 years (3 in the eradication treatment arm, 15 in the control arm), HR 0.21 [0.06 to 0.71], p = 0.013). (Supplementary Table S3, and Figure S4). The first episode of ulcer bleeding adjudicated as a primary outcome in the per protocol eradication treatment arm occurred at 525 days after randomisation vs 6 days for controls. A gastric ulcer was the underlying lesion in 22 (51 %) of patients experiencing a primary outcome (16 in the control arm, six in the eradication treatment arm (Supplementary Table S4),

Analysis of secondary outcomes

In an analysis restricted to hospitalisation due to gastric and duodenal ulcer bleeding the Cox proportional hazards assumption was also not met (Schoenfeld test p = 0.0115): there was a significant difference in outcome between treatment arms (HR 0.31, 0.11 to 0.85, p = 0.023) over the first 2.5 years but not thereafter (HR 1.10, 0.43 to 2.86, p = 0.84, Table 4, Supplementary Table S5 and Figure S5). For other secondary outcomes (other causes of clinically significant GI bleeding, clinically detected uncomplicated ulcers, thrombotic cardiovascular episodes) Cox proportional hazards assumptions were met: there were no significant differences between the treatment arms (Table 4, Supplementary Tables S8-S12 and Figures S4-S8). In the eradication arm 149 had a cardiovascular secondary outcome during follow-up, including 54 patients with CVA, 85 with MI, and 10 with both. In the control arm 169 patients had this outcome including 67 with CVA, 100 with MI, and 2 with both.

Prescriptions of aspirin fell progressively in both treatment arms during follow up (by 12.7% in the eradication arm and 12.3% in the control arm over the first 2.5 years) (Figure 3). The median duration of pre-trial aspirin prescription in patients who did not or did reach a primary outcome was 856 days (IQR 409,1298) vs 909 (388,1125) in controls, and 853 (419,1348) vs 815 (383,1181) in eradication patients respectively.
The point prevalence of PPI prescription increased (by 9.7% and 10.1% respectively in the eradication and control arms) over the first 2.5 years (Figure 3). Patients in the eradication arm were more likely to be prescribed NSAIDs (p=0.022) or PPIs (p=0.049 during follow-up (Table 4). Of the 44 patients with a primary outcome, 35 (79.5%) were still prescribed aspirin, 11 (25.0%) were prescribed a PPI and one patient in each treatment arm was prescribed an NSAID at the time of presentation. There were too few primary outcome events to power an analysis restricted to patients only prescribed aspirin, but analyses adjusted for time varying use of PPIs, H2RAs, antiplatelet medication, antacids and NSAIDs showed an unchanged pattern of results (HR over the first 2.5 years 0.33 [0.12 to 0.90], p = 0.03, Table 3, Supplementary Table S13). . None of the patients hospitalised for peptic ulcer bleeding had taken non-aspirin anti-platelet or anticoagulant medication in the year prior to presentation.

Exploratory analyses of the unexpectedly high number of patients in the control group with a negative end of study breath test. This may in part relate to home testing but there were showed apparent differences in drug exposure. Thirteen of the 41 control patients with a negative test (32%) had received clarithromycin during follow up compared to 9 of 127 (7%) of those with a positive breath test. Twelve of 39 breath test negative patients (31%) had been prescribed a PPI within the prior 90 days vs 10 of 127 (8%) with a positive test

There were 5307 patient reports of possible treatment related side effects that were like those already known (Supplementary Table S14). The commonest was taste disturbance. Three patients were hospitalised for a serious AE thought possibly related to study medication (detailed in Supplementary Table S15). In total 657 patients died during follow up (306 in the eradication treatment arm and 351 in the control arm). Only 2 of the 657 deaths were recorded by ONS as due to peptic ulcer (one due to bleeding). Fourteen patients with a primary outcome died during follow-up (6 eradication, 8 controls), at a median of 3.94 years (IQR 3.31 to 5.45) and 1.52 years (0.50 to 2.62) respectively after their presentation with peptic ulcer bleeding.

Discussion

In this large trial of patients taking low doses of aspirin chronically, we achieved high rates of *H. pylori* eradication and showed evidence of benefit with a 65% reduction in hospitalisation due to peptic ulcer bleeding over 2.5 years in patients in the eradication arm compared with the control arm. This was attributable to differences in gastric and duodenal ulcer bleeding. However, this advantage appeared to be lost subsequently. There was no significant difference in the incidence of uncomplicated ulcers or thrombotic cardiovascular events and the incidence of dyspepsia was low. As expected a substantial number of patients died but competing risks analysis showed our results for eradication treatment remained significant if adjusted for ongoing death rates. The large number of adverse events reported was expected, reflecting the active collection of data.

HEAT extends understanding of the effects of *H. pylori* eradication beyond the 12 months for which there were previous direct data and into the realm of primary prophylaxis. However, relatively few patients experienced ulcer bleeding and only two of the 657 patients who died had a death certificate citing peptic ulcer as the cause. A trend toward a lower death rate following eradication treatment was unexpected..

HEAT was a real-world study. Changes in prescribing including withdrawal of aspirin, or commencement of gastroprotective or ulcerogenic drugs were allowed as clinically indicated or recommended by consensus guidelines. However, differences between the treatment arms remained significant in analyses allowing for such drug use.. The number of control patients with a negative end of study breath test was higher than expected. Home breath testing has been shown to be reliable[27] but may yield false negatives but it is also plausible that exposure to clarithromycin and PPIs contributed, due to incidental eradication or suppression of *H. pylori*.

The loss of ulcer protection with time appears to be a real phenomenon that cannot be attributed to increasing use of gastroprotective drugs which would have an opposite effect. Possible causes could be enhanced acid secretion[33] or reduced release of protective prostaglandins[34] following *H. pylori* eradication. Another possibility is that *H. pylori* eradication uncovers a population of idiopathic ulcers with a high relapse rate[35].

Results for our main secondary analysis, involving bleeds from gastric and duodenal ulcers only, support the conclusion that our results are attributable to a reduced incidence of bleeding from gastric and duodenal ulcers, consistent with evidence that *H. pylori* does not promote and may even protect against oesophageal ulceration[36]. There were no differences between the treatment arms in the other secondary endpoints including uncomplicated ulcers. This probably relates to the different scenarios surrounding detection of bleeding and uncomplicated ulcers. Presentation with ulcer bleeding is involuntary because it is an emergency situation whereas the less pressing symptomology of an uncomplicated ulcer means some will go undetected, particularly if dyspepsia is not a prominent symptom, as was the case in HEAT.

Our results should be treated with some caution, given that the assumptions of proportional hazards were violated , requiring analysis over two time periods. We split follow up at the median of 2.5 years defined a priori to increase precision of estimates and minimise loss of power. This resulted in data that met the Cox proportional hazards assumption and revealed a significant difference between the treatment arms in the first period of follow up. The study was designed to be event driven and the sample size was based on a background rate of 8/1000 years of exposure over 2.5 years[22], but we observed a rate of only 2.67 /1000 person years in the control arm in the first 2.5 years of follow up. This is consistent with ONS mortality data showing a 2.5-to-3.4-fold reduction (from 1628 peptic ulcer deaths in 2001 to 641 in 2019 and 531 in 2020) during this century[37],,. In

addition, with changing guidelines, there has been a sharp decline in aspirin prescribing volumes amounting to a 35% reduction from a height of 33.4 million prescriptions in 2009 to 21.7 million prescriptions in 2019[38].

Our study had several strengths and limitations. It has authenticity as a pragmatic evaluation of the impact of *H. pylori* eradication in a large real-world cohort of patients chronically prescribed low dose aspirin. Its size, the high follow up rate for the primary outcome due to using national HES and ONS data, the very low number of withdrawals and effective blinding will have substantially reduced potential sources of bias. The ability to mount a study based on routine clinical data is a strength but at the potential loss of some precision. Its simplicity, which was fundamental to success involved some compromises, with potential confounding by use of other drugs. Access to comprehensive prescribing data is a mitigating strength and adjusting for drug use did not alter our results. We cannot confirm drug use as opposed to prescription, nor allow for over the counter use. The low rate of outcome events which led to the study being terminated before the planned number of primary outcome events had occurred is a limitation. In studying patients already taking aspirin we may have selected a low-risk population and excluded higher risk patients who had already bled when first prescribed aspirin**.** Establishment of a methodology for large outcomes studies in primary care widely supported by GPs is a strength, allowing use for other large studies including the ongoing ATTACK study in chronic kidney disease[39].

Our findings have potential clinical utility and can inform guideline development. However, the low rate of outcomes in HEAT, the likelihood that this may in part be related to use of protective treatments and the evidence that protection may be transient do not make a strong case to extend use of *H. pylori* eradication in the UK beyond high-risk patients. In the population of patients we studied, on average 238 (95%CI 184 to 1661) of them would need to be treated to avoid one hospitalisation for peptic ulcer bleeding. There may be a stronger case in countries with high persistent prevalence of *H. pylori.* A case can be made for a test and treat approach at the time of first prescription when there is probably a period of increased risk of peptic ulceration and gastrointestinal bleeding[6,40]. We did not find a difference in duration of prior aspirin prescription in patients who did or did not reach a primary endpoint. A previous cohort study reported that the risk of gastrointestinal bleeding in the first year after initiation of low dose aspirin was approximately double that seen in the subsequent seven years[6]. A recent study of two cohorts (UK Biobank and the German ESTHER cohort) found an increase in the incidence of gastric and duodenal ulcers in new but not prevalent users of aspirin[40].

Conversely, the low background rate of ulcer bleeding we found, together with availability of both *H. pylori* eradication and acid suppression as prophylaxis, should also inform assessment of the balance of risks and benefits of aspirin and may support a more liberal use. This should be factored into ongoing re-evaluations of the role of aspirin in cardiovascular disease[4,5] and possible extension into the prevention of colorectal and other cancers.[41]

4472 words

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Figure legends

Figure 1 Trial profile: CONSORT Diagram of patient distribution

Figure 2 Kaplan Meier curves for survival free of upper gastrointestinal ulcer bleeding. Inset shows data for first 2.5 years on an expanded scale

Figure 3 Six monthly point prevalence of aspirin, PPI and H2RA prescribing. Per cent of patients in each treatment arm on specified medication.
PPI: Proton pump inhibitor
H2RA: H2 receptor antagonist

Evidence in Context

Evidence before this study

Recent meta-analyses have shown that peptic ulcers and ulcer bleeding in patients prescribed low dose aspirin (≤325 mg daily) are strongly associated with *Helicobacter pylori*. This is compatible with the hypothesis that low dose aspirin acts to enhance bleeding from ulcers caused by *H. pylori* through its anti-haemostatic activity *H. pylori* eradication can prevent acute aspirin induced endoscopic injury, but data on secondary prevention of recurrent ulcer bleeding are contradictory. There have been no controlled trials of the effect of *H. pylori* eradication for primary prevention and none conducted in primary care

Added value of this study

This trial has shown that *H. pylori* eradication can be reliably achieved in large populations of unselected older patients using aspirin ≤ 325 mg in primary care. This is associated with a significant reduction in the risk of hospitalisation for ulcer bleeding, although this benefit is lost over time, something that has not been seen before

Implications of all the evidence

The establishment of *H. pylori* eradication as an alternative or addition to antisecretory protection adds to the gastroprotective strategies available for safe aspirin prescribing. The phenomenon of apparent lost protection warrants further investigation. Our findings should provoke a re-evaluation of strategies for the safe prescribing of aspirin and of the balance of risks and benefits of its use in cardiovascular disease and cancer prevention. The trial also establishes a methodology that can be applied to the evaluation in primary care of other significant clinical issues.

The HEAT Trialists: Members and functions

Trial Steering Committee

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Professor Tom MacDonald, University of Dundee
Mr Mike Bradburn, University of Sheffield
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Contributors
This study was conceived by CH and developed with AA, DK, FDRH (Hobbs), MM and GR, who were collaborators on the preparatory pilot studies, funded by MRC. They worked with JD, CACC (Coupland) and MS to finalize the detailed protocol. CACC and CC did the statistical analysis. JD and DS ran the study and wrote the two methodological papers. CM ran the software for the study within the secure NHS N3 network. CH wrote the first draft of the manuscript with input from CACC, CC, and JD. All authors participated in the interpretation of the data, and critical review of the manuscript. All authors have read and approved the final version.

Declaration of interests
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Data sharing.

We intend our data to be freely available, following publication subject to principles of confidentiality. Individual authors will notify CH as chief investigator of all approaches for sharing of data not in the public domain. CH will discuss with other authors where he judges there may be controversial or sensitive issues and if data are requested for other analyses, where it is likely that a protocol and signed data access agreement will be required.