Helicobacter pylori eradication for primary prevention of peptic ulcer bleeding in older patients prescribed aspirin in primary care (HEAT)

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

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Summary

Background Peptic ulcers in patients receiving aspirin are associated with *Helicobacter pylori* infection. We aimed to investigate whether *H pylori* eradication would protect against aspirin-associated ulcer bleeding.

Methods We conducted a randomised, double-blind, placebo-controlled trial (Helicobacter Eradication Aspirin Trial [HEAT]) at 1208 primary care centres in the UK, using routinely collected clinical data. Eligible patients were aged 60 years or older who were receiving aspirin at a daily dose of 325 mg or less (with four or more 28-day prescriptions in the past year) and had a positive C13 urea breath test for *H pylori* at screening. Patients receiving ulcerogenic or gastroprotective medication were excluded. Participants were randomly assigned (1:1) to receive either a combination of oral clarithromycin 500 mg, metronidazole 400 mg, and lansoprazole 30 mg (active eradication), or oral placebo (control), twice daily for 1 week. Participants, their general practitioners and health-care providers, and the research nurses, trial team, adjudication committee, and analysis team were all masked to group allocation throughout the trial. Follow-up was by scrutiny of electronic data in primary and secondary care. The primary outcome was time to hospitalisation or death due to definite or probable peptic ulcer bleeding, and was analysed by Cox proportional hazards methods in the intention-to-treat population. This trial is registered with EudraCT, 2011-003425-96.

Findings Between Sept 14, 2012, and Nov 22, 2017, 30 166 patients had breath testing for *H pylori*, 5367 had a positive result, and 5352 were randomly assigned to receive active eradication (n=2677) or placebo (n=2675) and were followed up for a median of 5·0 years (IQR 3·9–6·4). 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 incidence of the primary outcome in the active eradication group in the first 2·5 years of follow-up compared with the control group (six episodes adjudicated as definite or probable peptic ulcer bleeds, rate 0·92 [95% CI 0·41–2·04] per 1000 person-years *vs* 17 episodes, rate 2·61 [1·62–4·19] per 1000 person-years; hazard ratio [HR] 0·35 [95% CI 0·14–0·89]; p=0·028). This advantage remained significant after adjusting for the competing risk of death (p=0·028) but was lost with longer follow-up (HR 1·31 [95% CI 0·55–3·11] in the period after the first 2·5 years; p=0·54). Reports of adverse events were actively solicited; taste disturbance was the most common event (787 patients).

Interpretation *H pylori* eradication protects against aspirin-associated peptic ulcer bleeding, but this might not be sustained in the long term.

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Introduction

Aspirin is widely recommended for the secondary prevention of thrombotic vascular disease.[1–6] Its use is limited principally by increased risk of bleeding, particularly from the gastrointestinal tract.[7,8] Whether there is net benefit from aspirin in primary prevention of thrombosis is currently the subject of debate.[4,5] The risks of upper gastrointestinal bleeding can be mitigated in part by acid suppression with proton pump inhibitors and probably histamine H2-receptor antagonists.[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* might play a central role in the development of peptic ulceration[12–15] and ulcer bleeding[16–18] in patients receiving aspirin, but these data are largely observational and a causal role has not been established.

These studies suggest eradication of *H pylori* as a therapeutic target to prevent peptic ulceration and ulcer bleeding, 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 that the 6-month incidence

Research in context

Evidence before this study

We searched MEDLINE, PubMed, the Cochrane Database of Systematic Reviews, and the Database of Abstracts and Review of Effects, with no language or date restrictions, using the terms "aspirin", "*Helicobacter pylori*", and "peptic ulcer" before the study started and repeated the search on Oct 20, 2022. Meta-analyses have shown that peptic ulcers and ulcer bleeding in patients receiving 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. To our knowledge, there have been no randomised trials of the effect of *H pylori* eradication for primary prevention of aspirin-associated ulcer bleeding and no studies conducted in primary care.

Added value of this study

This trial showed that *H pylori* eradication can be reliably achieved in large populations of unselected older patients receiving aspirin at a dose of 325 mg or less in primary care. *H pylori* eradication was associated with a significant reduction in the risk of hospitalisation for ulcer bleeding, although this benefit was lost over time, a finding that has not been observed before.

Implications of all the available 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 over time 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 important clinical issues.

of ulcer rebleeding following *H pylori* eradication (1·9%) was not significantly different from that with proton pump inhibitor co-prescription (0·9%),[19] whereas another trial of 123 participants reported that 12-month rebleeding rates were significantly greater with *H pylori* eradication than with proton pump inhibitor 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,[21] while acknowledging that the evidence base for this recommendation is weak, observational, and based on indirect extrapolation. In view of these uncertainties, we aimed to investigate whether *H pylori* eradication would protect against aspirin-associated ulcer bleeding.

For more on **Docmail** see https://www.cfh.com/

See **Online** for appendix

Methods

Study design

We conducted a randomised, double-blind, placebo-controlled trial (Helicobacter Eradication Aspirin Trial [HEAT]) at 1208 primary care centres in the UK, using routinely collected clinical data: 1055 enrolled at least one trial participant. The study was conducted in accordance with International Council for Harmonisation guidelines and the Declaration of Helsinki, and was approved by the East Midlands—Leicester Central Research Ethics Committee (REC 11/EM/0434).

The trial was conducted using novel real-world methodology developed by the Simple Trials for Academic Research (STAR) group in Nottingham, UK. Following pilot funding from the Medical Research Council, a network of collaborating general practitioner investigators was developed.[22,23] The trial was coordinated from four UK research centres: Nottingham, Birmingham and Oxford, Durham, and Southampton. Participating 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 (Docmail) to invite them for trial participation. To maintain data security, the patient's National Health Service (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 National Institute for Health and Care Research (NIHR) research nurses at their general practice to check suitability, obtain informed consent, and perform an *H pylori* breath test (appendix p 3).

Participants

Men and women aged 60 years or older, who were receiving aspirin at a dose of 325 mg or less daily and who had received 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. Additional use of other antiplatelet agents was allowed. Patients who were receiving 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 an 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 (appendix pp 4–5).

H pylori status was determined using the Helicobacter Test INFAI,[24] performed by trained research nurses during the patient's screening visit (appendix p 3). 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 general practitioners were informed of their result.

Randomisation and masking

Eligible patients who had an unequivocally positive breath test were randomly assigned (1:1) to receive active *H pylori* eradication treatment (active eradication group) or placebo (control group). Randomisation was performed by the Nottingham Clinical Trials Unit using a validated, web-based system with separate sequences for each regional centre, using permuted blocks of randomly varying size. Participants, their general practitioners, health-care providers, the research nurses, trial team, adjudication committee, and analysis team were all masked to the treatment group allocation throughout the trial 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.

Procedures

Active treatment consisted of oral lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 400 mg, taken twice daily for 1 week.[25] Patients in the control group received oral placebo corresponding to each of the active treatments to be taken twice daily for 1 week. Active and placebo treatments (appendix p 3) 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 had no further trial visits after screening but were contacted annually to prompt reporting of any events. They remained under follow-up until the end of the trial (June 30, 2020) or until they died (from any cause) or withdrew consent for further use of their data. Patients 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 Feb 5 and Sept 6, 2019, to be done at home,[26] to assess the antibacterial efficacy of the eradication treatment.

Events during follow-up were identified from searches of Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality data, general practice databases using MIQUEST software,[26,27] and from patient and general practice spontaneous reports. For patients who moved to general practices not participating in the trial, 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 that mentioned gastrointestinal bleeding or peptic ulcer in any of these data sources were evaluated by a masked adjudication committee comprising three specialist clinicians (appendix p 3). A complete list of data from HES, supplied annually, covered the period from trial start (Sept 14, 2012) to finish (June 30, 2020). Primary care data were uploaded from individual practices intermittently. General practitioners were asked to do an end-of-study upload, but this was not always possible, in part because of disruption by the COVID-19 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 outcome was time to 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.[28] These criteria use the clinical presentation, its severity, and the endoscopic findings to generate a series of likelihood scenarios (appendix p 3). Secondary outcomes were 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 gastrointestinal bleeding, thrombotic cardiovascular outcomes, detected uncomplicated ulcers, number of general practice consultations for dyspepsia, and time to first prescription for proton pump inhibitor medication or other anti-ulcer or dyspepsia medication (H2-receptor antagonist, antacid, or alginate). Uncomplicated ulcers were those detected in the absence of clinically significant bleeding. Cardiovascular events were based on unadjudicated International Classification of Diseases-10 codes recorded in HES or ONS for myocardial infarction, cerebrovascular accident, and sudden cardiac death (appendix p 3).

Because patients only received 1 week of already well characterised treatment, and in conjunction with the Medicines and Healthcare products Regulatory Agency, we set a 4-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 adverse events reported by general practitioners outside this window were also collected as well as all deaths recorded by ONS.

Statistical analysis

We did an intention-to-treat analysis 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 had ulcer bleeding

between the screening visit and the randomisation date, and one patient who had not been 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 (HRs) and 95% CIs comparing treatment groups for the primary outcome. The assumption of proportional hazards was examined by a Schoenfeld test based on scaled Schoenfeld residuals and assessed graphically by a log–log plot.[29] Where there was clear evidence of violation of the proportional hazards assumption, HRs were calculated for separate periods of follow-up, split at the median time to event after randomisation. The number needed to treat to avoid one ulcer bleed was calculated using the time to event method described by Altman and Andersen.[30]

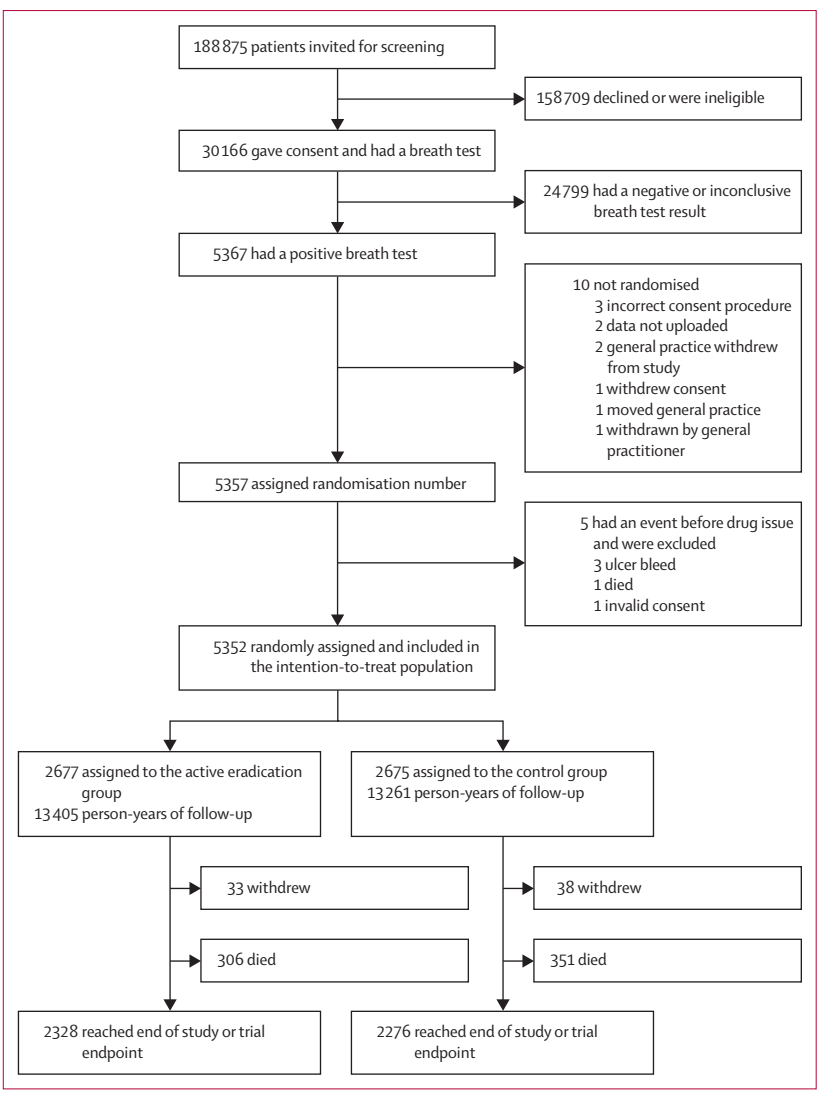

Figure 1: **Trial profile**

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-group 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.[31] We did a per-protocol analysis 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 hazards models. The numbers of general practitioner-recorded dyspepsia consultations during follow-up were compared between treatment groups using negative binomial regression to calculate rate ratios and 95% CIs accounting for overdispersion. Time to first prescription for proton pump inhibitor medication or other anti-ulcer or dyspepsia medication (H2-receptor antagonist, antacid, or alginate) during follow-up was compared between treatment groups using Cox proportional hazards models. The point prevalence of prescriptions for aspirin, proton pump inhibitors, and H2-receptor antagonists were estimated at 6-monthly timepoints throughout the study follow-up period.

The trial was intended to be event driven. On the basis of published data, we assumed an ulcer bleeding rate of eight events per 1000 patient-years in the control group.[22] To detect an HR of 0·50 comparing the intervention group versus the control group, 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 outcome 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 outcome events had occurred. Stata (version 17) was used for statistical analysis.

This trial is registered with EudraCT, 2011-003425-96.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 14, 2012, and Nov 22, 2017, participating general practices sent 188 875 invitation letters; 30 166 patients (16·0%) gave consent to trial participation and had an *H pylori* breath test, of whom 5367 (17·8%) had a positive result, 5357 were enrolled and assigned a randomisation number, and 5352 were randomly assigned (from one to 33 patients from each of 1055 general practices) to receive active eradication

(n=2677) or placebo (n=2675) and were included in the intention-to-treat population (figure 1).

Mean age at randomisation was 73·6 years (SD 6·9), 3948 (72·8%) of 5352 participants were male, and 1404 (26·2%) were female. The treatment groups were well balanced for ulcer risk factors and patient demographics (table 1). Coronary heart disease was the most common comorbidity among aspirin indications, followed by diabetes and a history of stroke or transient ischaemic attack (table 2). 540 (10·1%) of 5352 participants had been prescribed nitrates in the 90 days before randomisation, and less than 2% had a history of peptic ulcer. In the 10% retest sample of patients at a median of 3·95 years (IQR 2·76–5·28) after randomisation, 146 (90·7%) of 161 patients in the active eradication group had a negative breath test compared with 41 (24·0%) of 171 in the control group (p<0·0001).

Randomised patients were followed up for a total of 26 668 person-years (median 5·0 years [IQR 3·9–6·4]) 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 gastrointestinal bleeding: 44 patients had first episodes which were adjudicated as definite or probable peptic ulcer bleeds, 18 in the active eradication group and 26 in the control group (table 3).

Figure 2 shows Kaplan-Meier survival curves for the primary outcome, with early separation between the treatment groups. 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 groups early in the study, which was attenuated over time (figure 2; appendix p 6). Accordingly, we fitted one Cox model with time split in the data at the median of 2·5 years after randomisation, 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 and 21 episodes after 2·5 years. There was a significant reduction in incidence

	Active eradication group (n=2677)	Control group (n=2675)
Study centre		
Nottingham	672 (25·1%)	671 (25·1%)
Birmingham*	387 (14·5%)	383 (14·3%)
Durham	519 (19·4%)	516 (19·3%)
Oxford*	366 (13·7%)	370 (13·8%)
Southampton	695 (26·0%)	696 (26·0%)
Belfast†	27 (1·0%)	27 (1·0%)
Scotland†	11 (0·4%)	12 (0·4%)
Age at randomisation, years	73·5 (7·0)	73·7 (7·1)
Age group, years		
60–64	265 (9·9%)	267 (10·0%)
65–69	569 (21·3%)	576 (21·5%)
70–74	707 (26·4%)	644 (24·1%)
75–79	569 (21·3%)	616 (23·0%)
80–84	369 (13·8%)	377 (14·1%)
≥85	198 (7·4%)	195 (7·3%)
Sex		
Female	706 (26·4%)	698 (26·1%)
Male	1971 (73·6%)	1977 (73·9%)
Smoking status		
Non-smoker	1067 (39·9%)	1063 (39·7%)
Ex-smoker	1421 (53·1%)	1407 (52·6%)
Current smoker	184 (6·9%)	203 (7·6%)
Missing	5 (0·2%)	2 (0·1%)
Alcohol consumption		
No	731 (27·3%)	768 (28·7%)
Yes	1830 (68·4%)	1810 (67·7%)
Missing	116 (4·3%)	97 (3·6%)
Duration of aspirin use, days	853 (418–1346)	857 (409–1298)
Alcohol units per week‡	8·0 (3·0–16·0)	8·0 (3·0–16·0)
BMI	28·2 (4·8)	28·3 (4·9)
Index of multiple deprivation decile	7·0 (4·0–9·0)	7·0 (4·0–9·0)

Data are n (%), mean (SD), or median (IQR). *Birmingham and Oxford acted as a single centre. †Coordinated from Nottingham. ‡In patients reporting alcohol consumption.

Table 1: **Baseline characteristics**

	Active eradication group (n=2677)	Control group (n=2675)
Comorbidities recorded before randomisation		
Coronary heart disease	1285 (48·0%)	1347 (50·4%)
Stroke or transient ischaemic attack	355 (13·3%)	365 (13·6%)
Diabetes mellitus, any type	583 (21·8%)	625 (23·4%)
Diverticular disease	202 (7·5%)	183 (6·8%)
Dyspepsia	217 (8·1%)	216 (8·1%)
Peptic ulcer	48 (1·8%)	51 (1·9%)
Prescribed medications in the 90 days before randomisation		
Antacids	24 (0·9%)	17 (0·6%)
Antidepressants	85 (3·2%)	65 (2·4%)
Corticosteroids	49 (1·8%)	45 (1·7%)
Nitrates	274 (10·2%)	266 (9·9%)
Proton pump inhibitor*	72 (2·7%)	61 (2·3%)
H2-receptor antagonist*	4 (0·1%)	5 (0·2%)
Non-steroidal anti-inflammatory drugs	47 (1·8%)	43 (1·6%)
COX-2 inhibitors	2 (0·1%)	2 (0·1%)
Other antiplatelet or anticoagulant†	20 (0·7%)	18 (0·7%)

Data are n (%). *Exclusion criterion at baseline visit. †Included warfarin (n=17), dipyridamole (n=18), and ticagrelor (n=3).

Table 2: **Comorbidities and prescribed medications in randomised patients at baseline**

	Events		HR (95% CI); p value		
	Active eradication group	Control group	Adjusted for study centre as fixed effect	Adjusted for study centre, age, and sex	Adjusted for study centre and time-varying prescribed medications*
<2·5 years†	6; 0·92 (0·41–2·04)	17; 2·61 (1·62–4·19)	0·35 (0·14–0·89); p=0·028	0·36 (0·14–0·90); p=0·030	0·33 (0·12–0·90); p=0·030
≥2·5 years‡	12; 1·75 (0·99–3·08)	9; 1·33 (0·69–2·56)	1·31 (0·55–3·11); p=0·54	1·33 (0·56–3·15); p=0·52	1·16 (0·48–2·81); p=0·74

Data are number of events; rate per 1000 person-years (95% CI), unless otherwise stated. HR=hazard ratio. *Proton pump inhibitors, H2-receptor antagonists, aspirin, antacids, and non-steroidal anti-inflammatory drugs during follow-up. †During the first 2·5 years of follow-up. ‡After 2·5 years of follow-up.

Table 3: **Primary outcome event rates and HRs**

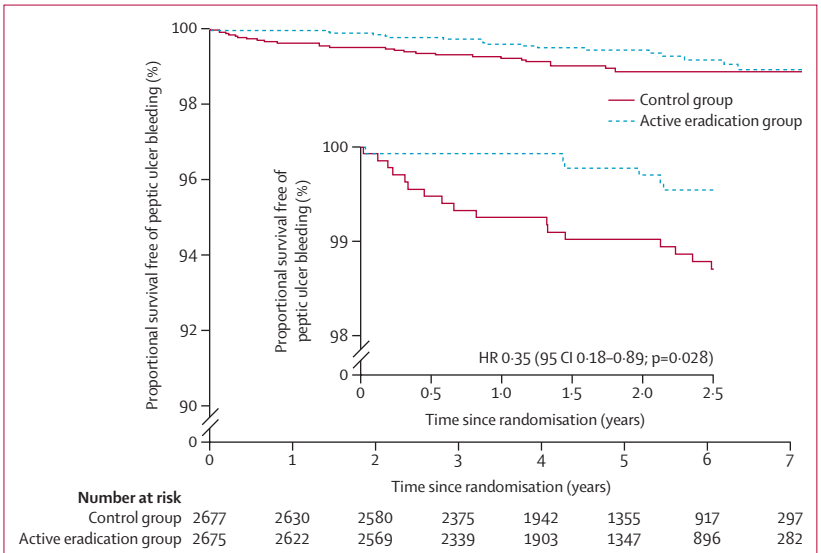

Figure 2: **Kaplan-Meier curves for survival free of peptic ulcer bleeding**
Inset graph shows first 2·5 years on an expanded scale. HR=hazard ratio.

of the primary outcome in the active eradication group in the first 2·5 years of follow-up compared with the control group (six episodes adjudicated as definite or probable peptic ulcer bleeds, rate 0·92 [95% CI 0·41–2·04] per 1000 person-years *vs* 17 episodes, rate 2·61 [1·62–4·19] per 1000 person-years; HR 0·35 [95% CI 0·14–0·89]; p=0·028; table 3). The number needed to treat was 238 patients (95% CI 184–1661). In the period after 2·5 years there were 12 episodes adjudicated as definite or probable peptic ulcer bleeds in the active eradication group (rate 1·75 [95% CI 0·99–3·08] per 1000 person-years) and nine episodes in the control group (rate 1·33 [0·69–2·56] per 1000 person-years; HR 1·31 [95% CI 0·55–3·11]; p=0·54; table 3). Results were similar after adjustment for age and sex. There was no significant interaction with age, although the low number of events limited the power for subgroup analyses.

A Fine-Gray model used to adjust for the competing risk of death showed the difference between the active eradication group and the control group remained significant in the first 2·5 years after randomisation (subdistribution HR within 2·5 years 0·35 [95% CI 0·14–0·89]; p=0·028; appendix p 7). In the per-protocol analysis of the 4369 patients who had received at least eight study treatment doses, there were 34 peptic ulcer bleeds adjudicated as primary outcomes, with 18 in the first 2·5 years (three in the active eradication group and 15 in the control group; HR 0·21 [95% CI 0·06–0·71]; p=0·013; appendix p 8). The first episode of ulcer bleeding adjudicated as a primary outcome in the per-protocol active eradication group occurred at 525 days after randomisation, compared with at 6 days in the control group. A gastric ulcer was the underlying lesion in 22 (51%) of 43 patients who had a primary outcome and had endoscopy investigation (16 in the control group and six in the active eradication group; appendix p 8).

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=0·012): there was a significant difference in incidence between the active eradication group and the control group (HR 0·31 [95% CI 0·11–0·85]; p=0·023) over the first 2·5 years but not thereafter (HR 1·10 [0·43–2·86]; p=0·84; table 4; appendix p 9). For other secondary outcomes (other causes of clinically significant gastrointestinal bleeding, clinically detected uncomplicated ulcers, and thrombotic cardiovascular episodes), Cox proportional hazards assumptions were met: there were no significant differences between the treatment groups (table 4; appendix pp 10–14). In the active eradication group, 149 patients had a cardiovascular secondary outcome during follow-up, including 54 patients with cerebrovascular accident, 85 with myocardial infarction, and ten with both, compared with 169 in the control group, including 67 with cerebrovascular accident, 100 with myocardial infarction, and two with both.

Prescriptions of aspirin decreased progressively in both treatment groups during follow-up (by 12·7% in the active eradication group and 12·3% in the control group over the first 2·5 years; figure 3). The median duration of aspirin prescription before the trial in patients who did not reach a primary outcome was 856 days (IQR 409–1298) in the control group versus 853 days (419–1348) in the active eradication group, and in patients who did reach a primary outcome was 909 days (388–1125) in the control group versus 815 days (383–1181) in the active eradication group.

The point prevalence of proton pump inhibitor prescription increased (by 9·7% in the active eradication group and 10·1% in the control group) over the first 2·5 years (figure 3). Patients in the active eradication group were more likely to be prescribed NSAIDs (p=0·022) or proton pump inhibitors (p=0·049) during

	Events		Proportional hazards assumption p value	Main analysis*		Secondary analysis†	
	Active eradication group	Control group		HR (95% CI)	p value	HR (95% CI)	p value
Gastroduodenal ulcer bleeding	14	24	0·012§	..	..	..	..
<2·5 years	5	16	..	0·31 (0·11–0·85)	0·023	0·32 (0·12–0·86)	0·025
≥2·5 years	9	8	..	1·10 (0·43–2·86)	0·84	1·12 (0·43–2·90)	0·82
Other clinically significant causes of gastrointestinal bleeding¶	51	46	0·42‡	1·10 (0·74–1·64)	0·64	1·11 (0·74–1·65)	0·61
Detected uncomplicated ulcers	67	66	0·57‡	1·01 (0·72–1·42)	0·97	1·01 (0·72–1·42)	0·96
Dyspepsia recorded by general practitioner‖	68	66	..	1·04 (0·70–1·54)	0·85	1·05 (0·70–1·55)	0·82
Cardiovascular outcomes	149	169	0·20‡	0·87 (0·70–1·09)	0·23	0·88 (0·71–1·10)	0·27
Medications with one or more prescriptions							
Proton pump inhibitor	1011	947	0·29‡	1·09 (1·00–1·19)	0·049	1·09 (1·00–1·19)	0·048
H2-receptor antagonist	101	87	0·20‡	1·16 (0·87–1·55)	0·30	1·17 (0·88–1·56)	0·28
Antacids	106	105	0·090‡	1·02 (0·78–1·33)	0·91	1·02 (0·78–1·34)	0·89
Non-steroidal anti-inflammatory drugs	468	406	0·82‡	1·17 (1·02–1·33)	0·022	1·16 (1·02–1·33)	0·025
Aspirin prescription stopped**	1150	1182	0·98‡	0·98 (0·91–1·07)	0·71	0·99 (0·91–1·07)	0·73

Data are n unless otherwise stated. HR=hazard ratio. *Adjusted for study centre as fixed effect. †Adjusted for study centre, age, and sex. ‡Proportional hazards assumptions valid: results are for whole follow-up. §Proportional hazards assumptions violated: results are for first 2·5 years of follow-up. ¶Cause of hospitalisation. ‖Rate ratio from negative binomial model. **Missed at least 90 consecutive days of prescription.

Table 4: **Secondary outcome events and HRs**

follow-up than those in the control group (table 4). Of the 44 patients who had a primary outcome event, 35 (79·5%) were still prescribed aspirin, 11 (25·0%) were prescribed a proton pump inhibitor, and one in each treatment group 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 proton pump inhibitors, H2-receptor antagonists, antiplatelet medication, antacids, and NSAIDs showed an unchanged pattern of results (HR over the first 2·5 years 0·33 [95% CI 0·12–0·90]; p=0·030; table 3; appendix p 15). None of the patients hospitalised for peptic ulcer bleeding had taken non-aspirin antiplatelet or anticoagulant medication in the year before presentation.

Exploratory analyses showed an unexpectedly high number of patients in the control group with a negative breath test at the end of the study. This finding might in part relate to home testing, but there were also apparent differences in drug exposure. 13 (32%) of the 41 patients in the control group with a negative repeat breath test had received clarithromycin during follow-up, compared with nine (7%) of 127 with a positive repeat breath test. Furthermore, 12 (31%) of 39 patients with a negative repeat breath test had been prescribed a proton pump inhibitor within the previous 90 days, compared with ten (8%) of 127 with a positive repeat breath test.

There were 5307 patient reports of possible treatment-related adverse events that were similar to the known safety profile (appendix p 16). The most common adverse event was taste disturbance (787 patients). Three patients were hospitalised due to serious adverse events thought possibly related to study medication (two in the active eradication group [extreme stomach pain and arrythmia with hypertension] and one in the placebo group [oesophageal spasm]; appendix p 16). Overall, 657 patients died during follow-up (306 in the active eradication group and 351 in the control group). Only two of the 657 deaths were recorded by ONS as due to peptic ulcer (one due to bleeding). 14 patients who had a primary outcome event

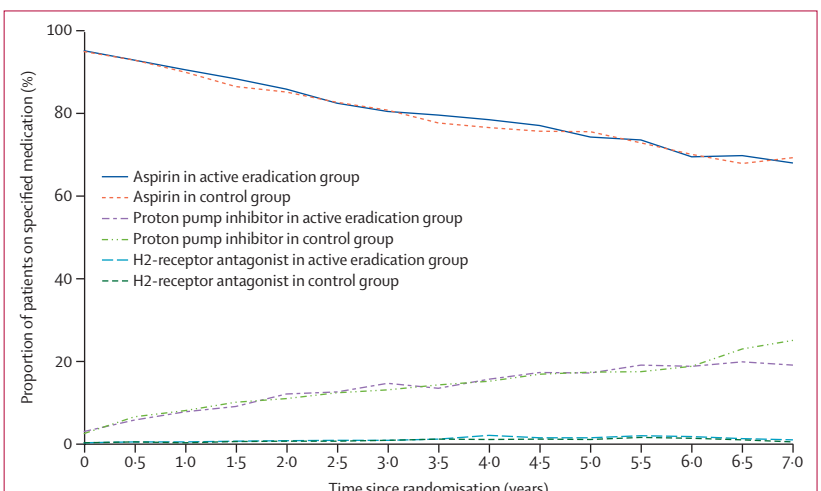

Figure 3: **6-monthly point prevalence of aspirin, proton pump inhibitor, and H2-receptor antagonist prescribing**

died during follow-up (six in the active eradication group, at a median of 3·94 years [IQR 3·31–5·45] after presentation with peptic ulcer bleeding; and eight in the control group, at a median of 1·52 years [0·50–2·62]).

Discussion

In this large trial of patients taking low doses of aspirin for several months in the previous year, we achieved high rates of *H pylori* eradication and showed evidence of benefit, with a 65% reduction in hospitalisations due to peptic ulcer bleeding over the first 2·5 years in patients in the active eradication group compared with the control group. This finding was attributable to differences in gastric and duodenal ulcer bleeding. However, this advantage appeared to be lost subsequently with longer follow-up. There was no significant difference between groups 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 when adjusted for ongoing death rates. The large number of adverse events reported was expected, reflecting the active collection of data.

This trial extends the 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 had ulcer bleeding, and only two of the 657 patients who died had peptic ulcer cited as the cause. A trend towards a lower death rate following eradication treatment was unexpected.

The HEAT trial was a real-world study, and 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 groups remained significant in analyses adjusting for such drug use. The number of patients in the control group with a negative repeat breath test at the end of the study was higher than expected. Home breath testing has been shown to be reliable,[26] but might yield false-negative results, and it is also plausible that exposure to clarithromycin and proton pump inhibitors contributed to this finding, 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[32] or reduced release of protective prostaglandins[33] following *H pylori* eradication. Another possibility is that *H pylori* eradication uncovers a population of idiopathic ulcers with a high relapse rate.[34]

Results from our main secondary analysis, including 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 might even protect against, oesophageal ulceration.[35] There were no differences between the treatment groups in the other secondary outcomes, including uncomplicated ulcers, which 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 urgent symptomology of an uncomplicated ulcer means some will go undetected, particularly if dyspepsia is not a prominent symptom, as was the case in our trial.

Our results should be interpreted 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 groups 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 events per 1000 person-years of exposure over 2·5 years,[22] but we observed a rate of only 2·67 events per 1000 person-years in the control group in the first 2·5 years of follow-up. This finding is consistent with ONS mortality data showing a 2·5–3·4 times reduction in peptic ulcer deaths (from 1628 peptic ulcer deaths in 2001 to 641 in 2019 and 531 in 2020) during this century.[36] Additionally, with changing guidelines, there has been a sharp decline in aspirin prescribing volumes, amounting to a 35% reduction from 33·4 million prescriptions in 2009 to 21·7 million prescriptions in 2019.[37]

Our study has several strengths but also some limitations. It has authenticity as a pragmatic evaluation of the impact of *H pylori* eradication in a large, real-world cohort of patients prescribed low-dose aspirin for at least several months of the previous year. The trial's 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 masking 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. The simplicity of the trial, 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 medication 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 might have selected a low-risk population and excluded patients who would

have been at higher risk who had already bled when first prescribed aspirin. Establishment of a methodology for large outcome studies in primary care widely supported by general practitioners is a strength, and allows for use of the methodology for other large studies, including the ongoing ATTACK study in chronic kidney disease.[38]

Our findings have potential clinical use and can inform guideline development. However, the low rate of outcomes in the HEAT trial, the likelihood that it might in part be related to use of protective treatments, and the evidence that protection might be transient do not make a strong case to extend use of *H pylori* eradication in the UK beyond patients at high risk of peptic ulcer bleeding. In the population of patients we studied, on average, 238 (95% CI 184–1661) would need to be treated to avoid one hospitalisation due to peptic ulcer bleeding. There might be a stronger case for extending eradication treatment 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.[6,39] We did not find a difference in duration of previous aspirin prescription between patients who did reach a primary endpoint and those who did not. 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 7 years.[6] A 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.[39]

Conversely, the low background rate of ulcer bleeding in our trial, 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 might support a more liberal use of the drug. Such information should be factored into re-evaluations of the role of aspirin in cardiovascular disease[4,5] and possible extension into the prevention of colorectal and other cancers.[40]

The HEAT Trialists

Trial Steering Committee: Prof David Mant (University of Oxford [Chair]), Prof Alex Ford (University of Leeds), Prof Tom MacDonald (University of Dundee), Mike Bradburn (University of Sheffield), Claire Ward (lay representative), Angela Shone (sponsor representative, University of Nottingham), Jennifer Dumbleton (University of Nottingham), Prof Chris Hawkey (University of Nottingham), Prof Richard Hobbs (University of Oxford), Prof Denise Kendrick (University of Nottingham). Independent Data Monitoring Committee: Prof Richard Logan (University of Nottingham), Prof Kenneth McColl (University of Glasgow), Prof Jon Deeks (University of Birmingham). Adjudication Committee: Prof Andrew Goddard (University of Derby), Richard Stevens (University of Oxford), Sarmed Sami (University College London). Regional support: Prof Margaret Cupples (Belfast), John Haughney (Glasgow). HEAT Trial Executive Team: Jennifer Dumbleton, Monique Morar, Diane Stevenson, Vic Shepherd, and Joanne Del Buono (Nottingham); Wendy O'Brien and Sharon Mckechnie (Southampton); Rachel Iles and Mina Davoudianfar (Oxford and Birmingham); and Andrew Moreton (Durham). Trial pharmacist: Sheila Hodgson (Nottingham).

Contributors

This study was conceived by CH and developed with AA, DK, FDRH, MM, and GR, who were collaborators on the preparatory pilot studies, funded by the Medical Research Council. They worked with JD, CACC, and MS to finalise 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 National Health Service N3 network. CACC, CC, and JD had access to and verified the data. CACC and CC did the statistical analysis. 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 of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

CH reports research funding from the Cancer Research UK AsCaP Catalyst Collaboration (A24991), and consulting fees from Kallyope. CH and JD report research funding from the UK National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme for the ALL-HEART (11/36/41) and ATTACK (16/31/127) studies. FDRH reports part-funding from the NIHR School for Primary Care Research, the NIHR Collaboration for Leadership in Health Research and Care (CLARHC) Oxford, the NIHR Oxford Biomedical Research Centre (BRC), and the NIHR Oxford Medtech and In-Vitro Diagnostics Co-operative. GR chairs and has received funding from the CanTest Collaborative, a Cancer Research UK Catalyst programme of research (C8640/A23385). AA is National Clinical Director for Prescribing (National Health Service England). All other authors declare no competing interests.

Data sharing

We intend for 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 might 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. Data requests should be sent to the corresponding author.

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