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CJ Hawkey, Anthony J Avery, Carol AC Coupland, Colin J Crooks, Jennifer S Dumbleton, FD Richard Hobbs, Denise Kendrick, Michael Moore, Clive Morris, Gregory Rubin, Murray Smith and Diane Stevenson on behalf of the HEAT trialists

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Extended Research Article

Eradication of *Helicobacter pylori* for prevention of aspirin-associated peptic ulcer bleeding in adults over 65 years: the HEAT RCT

CJ Hawkey[1*] Anthony J Avery[2] Carol AC Coupland[2] Colin J Crooks[1] Jennifer S Dumbleton[1] FD Richard Hobbs[3] Denise Kendrick[2] Michael Moore[4] Clive Morris,[5] Gregory Rubin[6] Murray Smith[7] and Diane Stevenson[1] on behalf of the HEAT trialists

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This article

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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 was a randomised placebo-controlled trial (European Union Drug Regulating Authorities Clinical Trials 2011-003425-96), conducted in United Kingdom primary care using routinely collected clinical data. Consenting participants 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 500 mg, metronidazole 400 mg and lansoprazole 30 mg, or placebos twice daily for 7 days. The primary outcome, time to death or hospitalisation due to peptic ulcer bleeding, was analysed using a Cox proportional hazards model.

Findings: Between 14 September 2012 and 22 November 2017, 30,166 participants underwent *H. pylori* breath testing, 5367 had a positive result, 5352 were randomised to an intention-to-treat population of 2677 (eradication) and 2675 (placebo) and followed up for a median of 5.0 years (interquartile range 3.9–6.4). Statistical analysis of the primary outcome showed an overall hazard ratio of 0.69 [95% confidence interval 0.38 to 1.25; $p = 0.22$], but there was a significant departure from the proportional hazards assumption ($p = 0.0068$), requiring analysis split at the median time to event: 2.5 years. There was a significant reduction in the primary outcome in the eradication treatment group in the first 2.5 years (hazard ratio 0.35, 95% confidence interval 0.14 to 0.89; $p = 0.028$) but not the second period (hazard ratio 1.31, 95% confidence interval 0.55 to 3.11). The number needed to treat (first period) was 238 (95% confidence interval 184 to 1661). Results in the first 2.5 years remained significant when accounting for the competing risk of death ($p = 0.028$). During the study period, 657 participants died (306 in the eradication group and 351 in the controls group; hazard ratio 0.86, 95% confidence interval 0.74 to 1.01; $p = 0.058$). Malignancy was the most common cause of death and largely accounted for the numerical difference between the treatment groups.

A health economic analysis found proactive screening not cost-effective, since the monetised benefits of the intervention in preventing a peptic ulcer bleed failed to outweigh the costs.

Interpretation: *Helicobacter pylori* eradication protects against aspirin-associated peptic ulcer bleeding, but this may not be sustained or cost-effective when applied non-selectively to our study population. The possibility that *H. pylori* eradication, on a background of aspirin use, might affect death from malignancies warrants further evaluation.

Limitations and future work: Studying subjects already established on aspirin probably contributed to the low event rate. A future study should investigate subjects starting on aspirin when the event rate is higher.

Trial registration: This trial is registered as ISRCTN10134725; ClinicalTrials.gov number NCT01506986.

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Report Supplementary Material 9 Assumptions underlying power calculations

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/LLKF7871).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
AES	Advanced Encryption Standard
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events
ASCEND	A Study of Cardiovascular Events in Diabetes
ASPREE	Aspirin Reducing Events in the Elderly
ATT	Antithrombotic Treatment Trialists
ATTACK	Aspirin To Target Arterial Events in Chronic Kidney Disease
CCG	Clinical Commissioning Group
CSV	comma-separated values
CV	cardiovascular
CVD	cardiovascular disease
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GI	gastrointestinal
GP	general practitioner
H2RA	histamine2 receptor antagonist
HEAT	*Helicobacter* Eradication Aspirin Trial
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IDMC	Independent Data Monitoring and Ethics Committee
ITT	intention to treat
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
NCTU	Nottingham Clinical Trials Unit
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	net monetary benefit
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
ONS	Office for National Statistics
pa	per annum
PPI	proton pump inhibitor
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAP	statistical analysis plan
TIA	transient ischaemic attack
TSC	Trial Steering Committee
UGIB	upper gastrointestinal bleeding

Note on currency

US$1 = £0.78 (date of conversion: 26 March 2025)

Plain language summary

Background

Low-dose aspirin is valuable in protecting people at increased risk from having heart attacks and strokes, but increases the risk of bleeding, particularly from stomach ulcers. The main cause of stomach ulcers is the bacteria *Helicobacter pylori*. We carried out a trial to test whether antibiotic treatment to eradicate *Helicobacter pylori* would protect participants from ulcer bleeding.

Methods

General practitioners in 1208 United Kingdom general practices searched their records to find people aged 60 and over who were taking low-dose aspirin. We used a breath test to detect *H. pylori* infection. Those with a positive result were randomly assigned to receive well-established eradication treatment with two antibiotics (clarithromycin and metronidazole) and a drug that reduces stomach acidity (lansoprazole), or matching placebos (dummy pills) twice daily for a week. We used routinely collected general practitioner and hospital data and death certificates to see if the treatment reduced the outcome of hospitalisation or death from ulcer bleeding.

Findings

We breath tested over 30,000 people. Over 5000 tested positive and were randomly assigned to receive active treatment (2677 people) or placebos (2675 people). Over an average of 5 years' follow-up, 44 people were hospitalised because of ulcer bleeding. People who had received active treatment were 65% less likely to develop ulcer bleeding in the first 2.5 years compared to those who had received placebos. However, this benefit reduced after longer follow-up, and there was no difference between the treatments when data from beyond 2.5 years were included in the analysis. *H. pylori* eradication was not cost-effective because of the large number of subjects that needed to be treated to prevent one ulcer bleed.

Conclusion

Helicobacter pylori eradication protects against ulcer bleeding in people on aspirin, but this may not be sustained.

Scientific summary

Aspirin in low doses (≤ 325 mg daily) is useful in reducing the risk of myocardial infarction (MI) and thrombotic stroke, but its use is limited by adverse events (AEs), principally bleeding, from the gastrointestinal (GI) tract. Meta-analyses show that peptic ulcers and upper gastrointestinal bleeding (UGIB) that occur in patients on aspirin are associated with *Helicobacter pylori* infection. Two studies of eradication in aspirin users who have already presented with an ulcer bleed have yielded inconsistent results, and there are no data on the effect of *H. pylori* eradication on ulcer bleeding at a population level. We therefore investigated the hypothesis that *H. pylori* eradication would protect against aspirin-associated ulcer bleeding.

Methods

The *Helicobacter* Eradication Aspirin Trial (HEAT) was a randomised placebo-controlled trial conducted in UK primary care which used routinely collected clinical data to identify possible participants and to follow clinical progress. It was conducted in 1208 UK primary care practices, of which 1055 enrolled at least one participant.

Recruitment

Consenting participants aged ≥ 60 years who were prescribed aspirin (≤ 325 mg) but not ulcerative or gastroprotective medication made a single baseline trial visit for collection of clinical data and underwent a C13 urea breath test for *H. pylori*. Those with a positive test were randomised to receive either a combination of clarithromycin 500 mg, metronidazole 400 mg and lansoprazole 30 mg or placebo twice daily for 7 days. Participants were asked to record the timing of each dose and record all possible side effects. Those recording taking at least eight doses formed the per-protocol population.

Follow-up

Outcomes were ascertained from electronic general practice records, Hospital Episode Statistics (HES) and Office for National Statistics mortality data. A randomly selected sample underwent repeat breath testing at the end of the study.

Outcomes

The primary outcome was time to hospitalisation or death due to definite or probable peptic ulcer bleeding (including gastric, duodenal and oesophageal ulcer bleeds). All plausible events which mentioned GI bleeding or peptic ulcer in any of the outcome data sources were evaluated by a blinded adjudication committee comprising three specialist clinicians.

The initial published protocol omitted to mention death due to peptic ulcer bleeding, noted while planning the statistical analysis after the trial had finished, but before the code was broken. Both hospitalisation and death categories were then explicitly included in the primary outcome in the planned analysis, although there were in fact no pre-hospitalisation peptic ulcer deaths.

Secondary outcomes were hospitalisation or death from gastroduodenal ulcer bleeds (oesophageal lesions excluded), clinically evident bleeds from other conditions, uncomplicated ulcers, consultations for dyspepsia, changes in selected drug prescription and thrombotic cardiovascular (CV) outcomes.

Statistics and power

An intention-to-treat (ITT) analysis was carried out including all randomised participants irrespective of whether they took the treatment, or the number of doses taken. The analysis of the primary outcome was based on time to first event. A Cox proportional hazards model adjusted for regional centre as a fixed effect was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) comparing the two treatment groups. The assumption of proportional hazards was tested using scaled Schoenfeld residuals and assessed graphically by a log minus log plot. Where there was clear evidence of violation of this assumption, HRs were calculated for two separate periods of follow-up split at the median time to event after randomisation.

To calculate sample size, we assumed a background event rate of 8/1000 ulcer bleeds per year and hypothesised that eradication treatment would reduce this by 50%. In order to detect this effect with 90% power, 87 primary outcome events were required. Primary outcomes occurred at a slower rate than expected, and the trial was stopped after 44 outcomes had occurred.

Results

Between 14 September 2012 and 22 November 2017, 30,166 participants underwent breath testing, of whom 5367 had a positive result and 5352 were randomised to an ITT population of 2677 (eradication treatment) and 2675 (placebo).

Baseline characteristics

Median age at consent was 73.6 (standard deviation 6.9) years, and 72.8% of the participants were male. Coronary heart disease was the most common comorbidity among aspirin indications (49.2%), and 10.0% were taking nitrates. More than half the participants (52.8%) were ex-smokers, but a history of peptic ulcer was uncommon (1.8%).

Treatment adherence

Treatment diaries were not returned by 432 participants (16.1%) in the control group and 418 (15.6%) in the eradication group. Of the 2675 participants in the control group, 2133 (79.7%) returned a record of having taken all 14 doses, and 2226 (83.2%) reported taking at least 8 doses. Fewer participants in the eradication group reported adherence to treatment: 1966 (73.4%) took all 14 doses, and 2143 (80.1%) reported taking at least 8 doses ($p = 0.003$ vs. controls).

Follow-up rates

Randomised participants were followed up for a total of 26,668 person-years [median 5.0 years, interquartile range (IQR) 3.9–6.4 years]. Seventy-one participants (1.3%) withdrew consent to further data follow-up at a median value of 503 days (IQR 69–1324) after randomisation.

Helicobacter pylori clearance

In the 10% sample of participants receiving a repeat breath test, a median of 3.95 (IQR 2.76–5.28) years after randomisation, the test was negative in 146 of 161 participants in the eradication group (90.7%) versus 41 of 161 (24.0%) in the control group ($p < 0.001$).

Primary outcome

In total, 44 participants had an episode that was adjudicated as a primary outcome, comprising 18 in the active eradication group and 26 in the control group. The overall HR comparing the eradication treatment group with the control group was 0.69 (95% CI 0.38 to 1.25; $p = 0.22$), but a Schoenfeld analysis showed a deviation from the proportional hazards assumption ($p = 0.0068$). Accordingly, we fitted one Cox model with a time split in the data at the median of 2.5 years' follow-up. This resulted in the Cox proportional hazards assumptions being met ($p = 0.54$ for the overall model). Two and a half years were selected prior to the unblinding of the data as the time point, with equal numbers of events and follow-up in both periods.

Primary end point: split time analysis

There were 23 episodes of the primary outcome of ulcer bleeding in the first 2.5 years (6 in the eradication group and 17 in the control group), with a rate of 0.92 (95% CI 0.41 to 2.04) per 1000 person-years in the eradication group and 2.61 (95% CI 1.62 to 4.19) per 1000 person-years in the control group. In the ITT analysis, there was a significantly reduced HR in the first 2.5 years for eradication treatment versus control of 0.35 (95% CI 0.14 to 0.89; $p = 0.028$) and a number needed to treat (NNT) of 238 (95% CI 184 to 1661). There were 21 episodes (12 in the eradication group and 9 in the control group) for follow-up after 2.5 years, with no significant difference between groups [HR 1.31 (95% CI 0.55 to 3.11); $p = 0.540$].

In the per-protocol analysis of 4369 participants who had taken at least 8 doses of treatment, the rates in the first 2.5 years were 0.57 (0.18 to 1.76) per 1000 person-years in the eradication arm and 2.75 (1.66 to 4.56) per 1000 person-years in the control group, and the HR was 0.21 (95% CI 0.06 to 0.71; $p = 0.013$).

Sensitivity analyses

The ITT hazard reduction remained significant in sensitivity analyses adjusting for age and sex and for time-varying drug use as well as in a Fine–Gray analysis adjusted for the competing risk of death.

Secondary outcomes

Hospitalisation for gastric or duodenal ulcer bleeds

In an analysis restricted to participants with bleeding from gastric or duodenal ulcers (oesophageal ulcers excluded), the proportional hazards assumption was not met, and data were again analysed on a split time basis. In the first 2.5 years of follow-up, there were 5 hospitalisations for ulcer bleeding in the eradication group compared to 16 in the control group, with a significant HR of 0.31 (95% CI 0.11 to 0.85; $p = 0.023$).

Other secondary outcomes

For all other secondary analyses based on time to event, proportional hazards assumptions were supported so analyses covered the whole unsplit follow-up time. There were no significant differences between the two treatment groups for any of the following end points:

- **Other causes of GI bleeding:** there were 97 episodes of clinically evident GI bleeding from causes other than peptic ulcers, 51 (1.9%) participants in the eradication group versus 46 (1.7%) in the control group.
- **Uncomplicated ulcers:** there were 67 participants (2.5%) with an uncomplicated peptic ulcer in the eradication group compared to 66 (2.5%) in the control group.
- **Consultations for dyspepsia:** in the eradication group, 68 participants (2.5%) had between 1 and 5 primary care consultations for dyspepsia during follow-up compared to 66 (2.5%) in the control group.
- **CV outcomes:** there were 149 participants in the active eradication group (5.6%) who had a CV outcome (85 MI, 54 stroke, 10 both) versus 169 (6.3%) control participants (100 MI, 67 stroke, 2 both), with a HR of 0.87 (95% CI 0.70 to 1.09; $p = 0.23$).
- **Changes in drug use:** prescriptions of aspirin fell progressively throughout the follow-up period. After 2.5 years of follow-up, 82.4% of those in the eradication group and 82.6% in the control group were still taking aspirin. The point prevalence of proton pump inhibitor (PPI) prescription increased progressively throughout follow-up: after 2.5 years 12.5% and 12.3% of those in the eradication and control groups, respectively, were prescribed a PPI. Few participants received antacids or histamine2 receptor antagonists (H2RAs).

Adverse events

There were 5293 reports of AEs (4006 in the eradication group, 1287 in the control group) in the 4 weeks from the start of trial treatment. This high frequency of AEs reflects the proactive collection via participant completed diaries. The pattern of reported AEs was similar to that already recognised for the drugs used. The most common were taste disturbance, diarrhoea and abdominal pain.

Deaths

In total, 657 participants died during follow-up [306 in the eradication group and 351 in the control group (HR 0.86, 95% CI 0.74 to 1.01; $p = 0.058$)]. The numerical difference was largely attributable to deaths due to malignancy.

Health economics

Out of the primary outcome analysis, the estimate of the NNT to prevent one peptic ulcer bleed was 238. Consequently, the costs of preventing a single peptic ulcer bleed using the HEAT proactive screening intervention were now expected to be substantial, where the cost incurred to screen, test and treat just one person was approximately £40 in 2020–1 prices. We used a decision tree model to account for other elements of the intervention: people refusing invitations to screen, people screened but returning a negative breath test and therefore not treated, and people with treatment side effects. From it, the cost for proactive screening to prevent just one peptic ulcer bleed were estimated to exceed £58,000.

Two factors arising when a peptic ulcer bleed occurs are avoided under the intervention and therefore defray the prevention cost: (1) the monetised value of the patient loss [valued at the National Institute for Health and Care

Excellence (NICE) threshold £20,000/quality-adjusted life-year (QALY)] and (2) the cost of hospitalisation for a bleed. For the latter, HES data were used to obtain the mean cost of hospitalisation associated with the trial primary outcome: eradication £3790 (95% CI £2117 to £5462) and control £3326 (95% CI £2094 to £4559) which did not differ significantly (p = 0.657). The other, patient loss, was assessed to be £810 using an area under the curve approach, the data for which came from responses to EuroQol-5 Dimensions, five-level version (EQ-5D-5L) obtained from those selected into the 10% resample group. Neither (1) and (2) alone or in combination fail to outweigh the costs of prevention [i.e. net monetary benefit (NMB) is negative-valued] and thus proactive screening is here not judged to be cost-effective.

Discussion

This report describes the results of a clinical trial conducted in primary care and using routinely collected clinical data to assess the effects or *H. pylori* eradication on subsequent ulcer bleeding. This was assessed using hospitalisation or death due to peptic ulcer bleeding as the primary outcome. Omitting mention of death due to peptic ulcer bleeding from the protocol was an error, but it did not affect the analysis, as there were no pre-hospitalisation deaths. The incidence of outcome events was lower than anticipated, and the trial was stopped before the intended number had accrued. Nevertheless, the trial was able to detect a biphasic pattern of results during follow-up. In the first time period, set at the median of 2.5 years after randomisation, there was a significant 65% reduction in the primary outcome following eradication compared to control treatment, which was particularly evident in the first 17.5 months when none of the participants that had received active eradication treatment developed ulcer bleeding. Thereafter, there was a progressive development of ulcer bleeding so that in the period beyond 2.5 years, there was no significant difference between the two groups.

The trial was conducted at a time when prescribing policies and attitudes to aspirin and coprescription of protective drugs were changing. This could have confounded our results, but the differences between the two groups remained significant when adjusted for time-varying drug use as well as for age, sex and the competing risk of death.

The reasons for the loss of the early benefit of eradication at later time points are unclear. We cannot definitively rule out reinfection or recrudescence of *H. pylori* infection as the cause, although this would be unusual for adults in this situation. Similarly, the time course makes a persistent but ultimately transitory effect of lansoprazole from the eradication regimen unlikely. *H. pylori* provokes an inflammatory response and enhances release of protective mediators such as prostaglandins: this could be lost over time. *H. pylori* eradication can lead to both increased or decreased acid secretion, but there is no direct evidence to make these possibilities anything other than speculative.

The findings of HEAT extend the range of patients for whom *H. pylori* eradication is indicated from secondary prevention of recurrent bleeding to patients on aspirin chronically who have not yet had an ulcer bleed. However, most of these patients will not develop this outcome, so that the NNT is high, making an unselective test-and-treat strategy that is not cost-effective. *H. pylori* eradication should be reserved for patients at higher risk. Epidemiological evidence suggests that risks are high during the first year of starting aspirin. This would be an appropriate scenario for future research. However, the loss of benefit with time should be factored into policy and research protocols.

Among secondary end points, there was no significant difference in the incidence of uncomplicated ulcers or thrombotic CV events, and the incidence of consultations for dyspepsia was low: this may be because antisecretory drug use was an exclusion criterion which excluded those using these drugs for dyspepsia treatment.

This study has developed a novel infrastructure and shown that it can be used for therapeutic research in primary care. The study had some weaknesses, particularly relating to the problems of generating a sufficient number of primary outcome events. These were largely study specific. Building on experience from HEAT, improvements in methodology, particularly with regard to timely automated acquisition of data, mean that a resource for the effective conduct of large trials in primary care has been established.

Trial registration

This trial is registered as ISRCTN10134725; ClinicalTrials.gov number NCT01506986.

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Chapter 1 Background and rationale for the trial

Peptic ulceration and its complications of bleeding and perforation represented a major health concern during the twentieth century.[1–3] Aspirin in high anti-inflammatory doses was early recognised as ulcerogenic to the stomach,[4] as were non-steroidal anti-inflammatory drugs (NSAIDs),[5–7] a property attributable to their ability to inhibit prostaglandin synthesis.[6] The failure of their promise to be a safer form of aspirin-dominated research in the third quarter of the twentieth century until identification of *Helicobacter pylori* as a causal agent prompted a further understanding of ulcer pathogenesis and recognition that the twentieth century 'epidemic' of peptic ulceration was arguably a true epidemic in a cohort of individuals that had been infected in childhood and adolescence.[2]

Meanwhile, low-dose aspirin, repurposed as an antiplatelet agent[8] capable of protection against thrombotic cardiovascular diseases (CVDs),[9] was prescribed in ever-increasing amounts until 2009,[10] when the *Helicobacter* Eradication Aspirin Trial (HEAT) was proposed. Subsequently, the prescribing volumes have declined sharply,[10] reflecting better definition of the patient groups who do and do not derive net benefit and concerns about safety. By then, low-dose aspirin was recognised as a major cause of bleeding, particularly from the gastrointestinal (GI) tract.[11–15] Clinical trial evidence was emerging to show this could be reduced by use of proton pump inhibitors (PPIs),[16] but there have been concerns about long-term safety of this strategy.[17] Evidence had emerged linking aspirin-associated ulcers and ulcer bleeding with *H. pylori*[18] making eradication of infection a rational therapeutic target, that HEAT was established to investigate.

Low-dose aspirin reducing thrombotic cardiovascular events

In the 1950s, a Los Angeles family doctor, Lawrence Craven, proposed aspirin as a treatment to prevent thrombotic episodes.[19] This was based on the observation that use of aspirin-impregnated chewing gum for post-tonsillectomy pain was often accompanied by serious bleeding complications. His proposal met with little support, but with the developing understanding of the role of platelets in thrombosis and recognition that aspirin could inhibit platelet function resulted in a trial showing a (statistically insignificant) reduction in the primary end point of death (8.3% vs. 10.9%).[20] This trial was included in an early meta-analysis of six randomised controlled trials (RCTs), and this showed a significant 21% reduction in reinfarction.[21] Reductions in myocardial infarction (MI) or death by as much as 50% have been seen in some studies.[9,22,23] The influential Antithrombotic Treatment Trialists (ATT) Collaboration meta-analysis of 16 secondary prevention trials following MI, transient ischaemic attack (TIA) or stroke reported an average 20% reduction in major coronary events, stroke or serious vascular events.[22,23] Aspirin was associated with an increased risk of major (mainly GI) bleeding, but the benefits of aspirin exceeded risk. Results from trials of secondary prevention have consistently reported a beneficial reduction in thrombotic cardiovascular (CV) events of 10–20 per 1000 per annum (pa) at the expense of a 1–2 per 1000 increase in major bleeds, principally GI.[23] Consequently, aspirin has become widely recommended for secondary prevention of thrombotic CV events.[24–26]

Primary prevention

The role of aspirin as primary prevention against thrombotic vascular pathology has been much more difficult to establish.[9,23,27–36] In the six primary prevention studies included, in the original ATT meta-analysis, the absolute event rates in controls were much lower than in secondary prevention studies (0.57% pa vs. 8.2% pa). Although the proportional reduction with aspirin was comparable, the absolute benefit with aspirin was less in primary prevention studies (absolute event rates reduced by 0.06% pa to 0.51% pa) than in secondary prevention studies (absolute event rates reduced by 1.5–6.7% pa).[9,21–23] This pattern of results has been seen in subsequent studies, including three large landmark studies of enteric-coated aspirin 100 mg daily in primary prevention settings. The A Study of Cardiovascular Events in Diabetes (ASCEND) trial recruited patients with diabetes and found a 12% reduction in serious vascular events, but at the cost of a 30% increase in major bleeds (mainly GI).[28] The Aspirin to Reduce Risk of Initial Vascular

Events (ARRIVE) trial aimed to recruit patients with moderate CV risk (target 10–20% 10-year vascular risk) but, with a control event rate of 4.48% over 5 years, studied a lower-risk population than intended. There was an absolute reduction in serious vascular events (including TIA and unstable angina) of 0.19–4.29% over 5 years (not significant) and an increase in bleeding events from 0.46% to 0.97%.[29] Aspirin Reducing Events in the Elderly (ASPREE) investigated a composite of disability-free survival in patients aged 70 or over.[30,31] The study was abandoned for futility. Aspirin was associated with a significant increase in all-cause mortality, associated with an increase in cancer mortality and in major haemorrhage.

Data from these three trials, together with those from the 12 others in the literature, have been subjected to meta-analysis. Compared to control, aspirin was associated with reductions of 18% in non-fatal MI, 21% in TIA and 13% in ischaemic stroke. These benefits were counterbalanced by a 52% increase in major GI bleeding and 32% in intracranial haemorrhage.[32] Several more meta-analyses have been performed as more data emerge.[33,34] The most recent meta-analysis of 21 trials of 173,810 individuals with a mean follow-up 5.3 years found an 11% reduction in thrombotic outcomes, principally non-fatal MI and TIAs, with 48% increase in GI bleeding. As in earlier meta-analyses of smaller data sets, the risk of harm was greater than the chance of benefit,[35] and aspirin is not recommended for primary prophylaxis.[25]

Aspirin and cancer

There is currently significant interest in the possibility that aspirin may be able to prevent the development of colorectal[9,31,36–40] and possibly other cancers.[40] Much of the evidence comes from observational studies[9,31,36–40] and from reanalysis of CV trials.[41–45] Overall, these studies suggest that the incidence of colorectal cancer decreases after 3 or more years of aspirin use and remains detectable up to 4 years after aspirin cessation, with a reduction in mortality detectable at 5 years and lasting 10 years after aspirin cessation.[9,36,43–45] These studies have used a variety of dosing regimens, but a clear pointer to appropriate dosage has not emerged: some studies have used relatively high doses of aspirin, while in others, there was only benefit with the lower of two-dose regimens. They can also be criticised for lacking cancer as a prespecified end point, although it is difficult to identify an invalidating systematic bias across a large number of studies.

Arguably, more compelling evidence comes from prospective randomised trials of aspirin in hereditary non-polyposis colorectal carcinoma, also known as the Lynch syndrome. In CAPP-2, aspirin 600 mg daily was associated with a reduction in colon cancer, but only late after the trial had finished.[46,47] A delayed emergence of benefit is in keeping with data from other studies. However, Lynch syndrome accounts for only 3% of colorectal cancers, so the observed results may not be generalisable to sporadic colon cancers. A successor trial, CAPP-3, is evaluating lower doses. However, results from the ASCEND, ARRIVE and ASPREE trials cast some doubt on the efficacy of aspirin as an effective prophylaxis against colorectal and other cancers. In ASCEND, GI tract cancer was a prespecified end point, but there was no difference in the incidence of cancer or cancer-related mortality.[28] This was also the case in ARRIVE.[29] The biggest challenge to the notion of aspirin as an anticancer agent comes from ASPREE,[30,31] which reported a 31% increase in cancer-related mortality (but not cancer incidence). ASPREE has been criticised for making multiple unadjusted analyses. However, a recent meta-analysis of 13 primary CV prevention trials found no significant benefit for cancer-related survival, even when data from ASPREE were excluded.[9]

Need for gastroprotection

The principle on which use of aspirin for CV thrombotic or cancer prevention is based is that fewer patients should be harmed than are protected. For primary prevention of CV disease, the benefits are an order of magnitude lower than its use in secondary prophylaxis, while the harms are similar. Furthermore, although there is net benefit in most secondary prophylaxis scenarios, there is still significant residual harm. The risk of bleeding is high in new users.[13–15] Data on cancer are not sufficiently clear to tip the balance in favour of benefit, and the United States Preventive Services Task Force inclusion of cancer in its recommendation in 2016[24] has recently been withdrawn.[26] Thus, prevention of major GI bleeding becomes the key focus of attempts to improve net safety.

Gastroprotection with proton pump inhibitors

Between 2002 and 2016, 17 RCTs (6 from China) investigated PPIs for their ability to prevent ulcer formation and/or the development of upper gastrointestinal bleeding (UGIB) in patients with risk factors who were on aspirin.[48–51] These data were the subject of 3 meta-analyses published between 2015 and 2017 which compared normal doses of PPIs with placebo (5 studies), histamine2 receptor antagonists [H2RAs (10 studies)] or Gefarnate (2 studies).[48–51] Overall, PPIs were more effective than the comparator treatment, and there was evidence for effectiveness for each individual PPI (omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole). Although H2RAs have been supported as an alternative to PPIs, the weight of evidence suggests that they are less effective.[50]

Concerns about proton pump inhibitors

Several descriptive studies have raised quite numerous concerns of varying plausibility about possible adverse consequences of long-term use of PPIs.[17,52–54] These include salmonella and campylobacter infections occurring because of reduced ability to sterilise the gut.[52] This mechanism may also underlie pseudomembranous colitis due to *Clostridium difficile*, pneumonia, small intestinal bacterial overgrowth and spontaneous bacterial peritonitis, although associations between these conditions and PPI use are less consistent. Reduced acid could plausibly account for malabsorption of iron and vitamin B12. An important but as-yet-unresolved area of concern relates to the possibility that PPIs may increase the risk of fractures;[53] at present, it is not clear whether the association is causal because of alterations in mineral metabolism or non-causal, arising because PPIs are more likely to be used in patients otherwise predisposed to fractures. Other associations include episodes of acute interstitial nephritis, micronutrient deficiency and dementia. Although there has been long-term concern that acid suppression would enhance gastric cancer by intensifying inflammation and atrophy, and possibly other malignancies via hypergastrinemia and other systemic factors, this has not emerged as an outcome in RCTs.[17]

Although the causal nature of some of these associations can be questioned,[54] they are a legitimate cause for concern, particularly with long-term continuous use, such as those using PPIs to protect against GI bleeding. The issues outlined above which were current when HEAT was planned made *H. pylori* eradication an attractive potential alternative approach.

The case for *Helicobacter pylori* eradication

There is limited but coherent and convincing evidence that *H. pylori* may play a central role in the development of peptic ulceration[55–57] and ulcer bleeding[13–15,58] in patients taking aspirin. An endoscopic study of aspirin users found a point prevalence of 11% of (largely silent) gastric or duodenal ulcers. *H. pylori* increased risk by 5-fold (gastric or duodenal ulcers) and for duodenal ulcers specifically by 18.5-fold.[55] In a meta-analysis of 10 cross-sectional studies and 7 RCTs, the authors calculated that *H. pylori* increased ulcer risk by 70% or almost twofold in subjects not taking antisecretory drugs.[57] A meta-analysis of seven case–control studies of aspirin users found the risk of UGIB was increased with *H. pylori* with an odds ratio (OR) of 2.32 [95% confidence interval (CI) 1.25 to 4.33].[58]

These data are largely observational and do not establish a causal role. Intervention data comparing *H. pylori* eradication with controls are limited. In a small study of acute injury occurring in patients infected with *H. pylori* who were starting aspirin 300 mg, there was evidence of benefit in those that underwent eradiation. In the control group that received placebo eradication drugs, aspirin caused a rise in Lanza scores (from 0.69 ± 0.87 to 2.25 ± 1.3, $p < 0.0001$) at 4 months.[59] By comparison, in those that underwent successful *H. pylori* eradication, these changes were not significant (baseline score 0.43 ± 0.72 vs. 0.75 ± 0.93, after 4 months $p > 0.05$). Unfortunately, a direct comparison of changes between the two groups was not reported. Only four patients developed ulcers (three controls, one in the eradication group), and there were no episodes of GI bleeding.[60]

Randomised controlled trials where the end point is ulcer bleeding have been limited to secondary prevention of recurrent ulcer bleeding and have yielded discordant results.[60,61] One trial of 250 participants in Hong Kong, from Chan

and colleagues, reported a 6-month incidence of ulcer rebleeding following *H. pylori* eradication (1.9%) not significantly different from that with PPI coprescription (0.9%), while another trial of 123 participants, also from Hong Kong, reported 12-month rebleeding rates significantly greater than those with PPI coprescription (14.8% vs. 1.6%).[61]

While HEAT was ongoing, Chan extended this work in a non-randomised long-term study[62] in which three cohorts of patients were prescribed low-dose aspirin without PPI cover:

- Patients with ulcer bleeding and *H. pylori* infection who underwent eradication and healing before resuming aspirin.
- *H. pylori*-negative patients with ulcer bleeding who similarly underwent ulcer healing before resuming aspirin.
- Patients without a history of ulcer or ulcer bleeding who were starting aspirin for the first time and who were not tested for *H. pylori* (labelled Average Risk).

Over 5048 patient-years of follow-up (mean 5.5 years per subject), the mean incidence of ulcer bleeding in the *H. pylori* eradicated cohort was 0.97 per 100 patient-years, lower than in the *H. pylori* negative cohort (5.22/100 patient-years) and not significantly different from the average-risk cohort (0.66 per 100 patient-years). The lack of randomisation and differences in demographic features between the cohorts makes this study difficult to interpret and underlines the need for controlled data.

The lack of direct data on prevention of ulcer bleeding in the wider group of patients taking aspirin means that guidelines have been cautious and nuanced. The American College of Gastroenterology guidelines suggest testing for *H. pylori* when starting low-dose aspirin, while acknowledging that the evidence base for this recommendation is weak, observational and based on indirect extrapolation.[63] In view of these uncertainties, we conducted a large RCT of *H. pylori* eradication for the prevention of ulcer bleeding in patients aged ≥ 60 years who were prescribed aspirin. Although anti-inflammatory doses of aspirin are intrinsically ulcerogenic, the much lower doses used for prevention of thrombosis are less damaging, raising the possibility that aspirin's role is an antihaemostatic one,[64] enhancing bleeding in ulcerative lesions caused by other factors, principally *H. pylori* for the stomach and duodenum.

Chapter 2 Pilot study

Before starting the trial, we undertook literature searches using the following two strategies to identify the systematic published evidence. Reference numbers have been amended to fit current reference list, and last accessed dates in the reference list refer to the original trial proposal:

Strategy 1: 'Aspirin AND *Helicobacter pylori* AND (peptic ulcer OR stomach [gastric] ulcer OR duodenal ulcer) applied to the Cochrane Database of Systematic Reviews (www.cochranelibrary.com/cdsr/reviews)'; CRD Database of Abstracts and Review of Effects (DARE) [www.crd.york.ac.uk/crdweb/ (accessed 30 July 2025)], Ovid MEDLINE [https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi (accessed 30 July 2025)] and PubMed {limited by the term 'meta-analysis' [www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed& cmd=detailssearch&term=aspirin+AND +helicobacter+pylori+AND +peptic+ulcer+OR+gastric+ulcer+OR+ stomach+ulcer+OR+ duodenal+ulcer+AND+metaanalysis&log$=activity (accessed 7 February 2011)]} and via 'Systematic reviews' [www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&cmd=detailssearch&term=aspirin+AND+heli cobacter+AND+systematic%5Bsb%5D&log$=activity (accessed 7 February 2011)], supplemented by manual searching of Clinical Evidence (*BMJ*) [https://bestpractice.bmj.com/info/ (accessed 30 July 2025)] and the Gastroenterology section of the National Library of Health [www.library.nhs.uk (accessed 30 July 2025)].

Strategy 2: 'Peptic ulcer OR stomach ulcer OR duodenal ulcer (Prevention and Control, Therapy)' AND Aspirin was searched in Ovid MEDLINE [https://ovidsp.dc1.ovid.com/ovid-new-a/ovidweb.cgi (accessed 30 July 2025)].

These searches identified data quantifying risk and are supported by more recent meta-analyses, establishing a strong association between *H. pylori* and peptic ulcers and UGIB.[57,58] They were used in designing and powering HEAT, together with pilot studies.

The aims of the pilot phase were to:

1. Investigate the logistics of identifying large numbers of patients taking aspirin.
2. Evaluate use of general practitioner (GP) digital data and national sources of information for event data [digital.nhs.uk/services/terminology-and-classifications/read-codes (accessed 6 June 2023); www.statistics.gov.uk/statbase/Product.asp?Vlnk=14409 (accessed 7 February 2011); www.hesonline.nhs.uk/Ease/servlet/content-server?Siteid=1937&categoryid=214 (accessed 7 February 2011)].
3. Define response rates to an invitation to trial participation.
4. Compare types of enrolment strategies.
5. Investigate the logistics of screening large numbers of patients for *H. pylori* and treating those that were positive.
6. Identify the prevalence of *H. pylori* in such patients in different areas of the UK.
7. Define rates of *H. pylori* eradication in the proposed patient population (older patients prescribed aspirin).
8. Identify the willingness of such patients to enter a randomised study.
9. Identify the level of interest in the study from GPs.
10. Identify current rates of ulcer bleeding and the effect of aspirin on this.

These questions were addressed by piloting and optimising proposed trial protocols (non-randomised), by questionnaires to patients and GPs and by an analysis of epidemiology using the QResearch database [www.qresearch.org/sitepages/Home.aspx (Inactive)]. Our analysis of the QResearch database showed a 3.15-fold (95% CI 2.94 to 3.37) increase in risk of peptic ulcer bleeding associated with aspirin, compatible with data from our literature search [www.qresearch.org/sitepages/Home.aspx (Inactive)]. Risk increased with age, especially over age 60 years.

We invited 2525 patients to participate in a non-randomised study of *H. pylori* eradication: and 1196 (47.4%) volunteered and 825 (32.7%) enrolled, of whom 184 (22.3%) had a positive *H. pylori* breath test and were prescribed eradication therapy (clarithromycin 500 mg, metronidazole 400 mg and lansoprazole 30 mg all given twice daily for 7 days). This achieved a 91.3% eradication rate.[65] We noticed that patients from socially deprived areas had a higher rate of positive breath testing[66] and resolved to recruit such patients selectively in the main trial, in order to make our

data relevant to those most at need. For similar reasons, we took steps to make the trial attractive to practices that were not previously research active, by minimising unnecessary administrative burdens.

This exercise allowed us to model and optimise logistical aspects of the proposed study, including searching GP records for suitable patients, bulk mailing, conducting baseline visits, including breath testing and assessment of the proposed eradication regimen.[65,66] A number of changes to the original intended protocol were adopted, including the use of Docmail (www.docmail.co.uk)[67] for secure communication to patients. Following feedback from GPs and patients, the original intention to hold trial visits at a drop-in centre with instant breath test analysis on site was dropped in favour of clinic attendance at the GP surgery with commercially available kits and posted to a central assay facility. In response to a questionnaire, 72% of patients said they would enter a randomised placebo-controlled trial.

General practitioners from 63 practices were approached to assess interest in participating in the main study. Of these, 73.7% said they were likely or very likely to participate in the full randomised study.

Chapter 3 A facility for secure handling of large volumes of data

Large trials require substantial numbers of investigators and/or resource-intensive digital data management. Primary care with its comprehensive patient record is potentially a rich source of data for clinical trials. Conventional approaches to recruitment that rely on opportunistic identification of patients as they present to primary or secondary care are inefficient and also result in disruption to the clinical services where they are deployed. Effective recruitment of large numbers of patients is assisted when clinical and research recruitment activity are separated. By contrast, digital access to routinely held data can streamline identification of potential trial participants as well, enabling the collection of greater quantities of outcome data.

We chose to work with TCR Nottingham Ltd (Langley Mill, UK), a data management entity that works within the confidential NHS N3 digital network. TCR has been involved in providing data queries and desktop tools for general practice since 1990 and has also collaborated with researchers from the University of Nottingham, making them well placed to manage the development of the systems. An ability to interrogate all commonly used GP database systems was a major advantage.

The fact that data are held within the confidential N3 network was also critical to the trial's feasibility.

Support systems

There were three distinct elements involved in designing processes to support this study:

1. Data extraction – finding eligible patients to present to practices.
2. A software toolkit for the practices to manage the eligible patients.
3. A web application to allow the study team to manage the clinical trial.

Each of these solutions needed to be capable of large-scale deployment and, where possible, automation to reduce the time and effort spent by the many hundreds of individuals involved throughout the lifetime of the trial.

Data extraction

It was decided to use MIQUEST as the mechanism for data extraction. MIQUEST was a mandatory requirement for clinical systems and provided a reliable method for extracting data in a common format from the different clinical systems that were in use at the beginning of the trial [https://digital.nhs.uk/services/terminology-and-classifications/read-codes (accessed 6 June 2023)]. Clinical systems that did not have their own MIQUEST implementation were able to provide MIQUEST-compliant extractions using Quest Interpreter, a tool developed by TCR to help smaller system suppliers to achieve the MIQUEST standard and provided to them under license. MIQUEST uses Health Query Language (HQL) scripts to generate data extraction reports as comma-separated values (CSV) files.

The *Helicobacter* Eradication Aspirin Trial practice toolkit

TCR provided an electronic toolkit which could be downloaded from the TCR website and installed on a personal computer at the GP practice. This contains HQL query files which were used to search for patients meeting trial eligibility criteria and import a list of potential trial participants (as a CSV file), along with all of the clinical, laboratory and prescribing information trial that would be needed for those who would enter the trial.

An electronic screening log was created with a minimum data set comprising patient initials, year of birth and gender. To maintain data security, the patient's NHS number was encrypted to Advanced Encryption Standard (AES)256. AES256 is a virtually impenetrable symmetrical encryption algorithm that uses a 256-bit key to convert data into a cipher. The key used in HEAT to generate the unique identifier includes the NHS number itself, thus generating a unique secure identifier.

This encrypted minimum data set was uploaded to the trial database, and a screening number was generated. The list of potential trial participants was reviewed by the GP, and a CSV file of names and addresses of suitable patients was loaded into CFH Docmail, an electronic service which generated mail packs with trial information, an invitation to participate from the GP and a consent form to review. A dedicated telephone number was provided for interested patients to ring for any further information and to make an appointment to attend a baseline screening and enrolment clinic.

Once a patient had joined the study and given written permission to share the clinical data approved for the trial, the practice toolkit provided a mechanism to release the data to the study team. Once released, the toolkit established a secure connection to the study database. The data stream was pre-encrypted and sent via this link and stored (still encrypted) in the study database. This connection was also the mechanism for upload of data during trial follow-up.

The study database

A comprehensive browser-based system was developed to provide the database record of relevant clinical data (detailed in the *Report Supplementary Material 1*) and the key processes to manage patients through the trial, including:

- hosting within the N3 network
- notification when the practice sent invitations
- entering the patient's response
- a diary to schedule baseline visits for evaluation, consent and breath testing
- entering the data-capture details from the patient appointment
- randomisation of patients to either arm of the trial
- generation of letters to patients
- entering questionnaire responses
- providing a wide variety of reports and summaries to support the study
- user management and login security.

Trial database: confidentiality and security

Computer-held data, including the trial database, were held securely and password protected. All data were stored on a secure dedicated web server at King's Mill Hospital (within the N3 NHS Private Data Network). Access was restricted by user identifiers and secure passwords (using AES-25S encryption). User roles were assigned to determine the level of access within the database. Information about the trial in the participant's medical records/hospital notes was treated confidentially in the same way as all other confidential medical information stored on the N3 network.

Chapter 4 *Helicobacter* Eradication Aspirin Trial methods

Design, principles and governance

The HEAT was a double-blind randomised placebo-controlled study (European Union Drug Regulating Authorities Clinical Trials number 2011-003425-96, ICTRN ISRCTN10134725) 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 (HTA) programme of the UK's National Institute for Health and Care Research (NIHR). It was developed with involvement from the start of two lay members, with continuing involvement of one of them as a member of the Trial Steering Committee (TSC). The trial was undertaken in accordance with International Conference on Harmonisation guidelines and the Declaration of Helsinki and was approved by East Midlands, Leicester Central Research Ethics Committee (REC 11/EM/0434). The TSC was constituted according to NIHR guidelines and delegated day-to-day management to a project management group, organised by the trial manager under the direction of the trial chief investigator. The trial was also overseen by a three-person Independent Data Monitoring and Ethics Committee (IDMC) which had access to partially unblinded (Group A and Group B) data.

Recruitment

Helicobacter Eradication Aspirin Trial was conducted using novel real-world methodology developed by the Simple Trials for Academic Research group in Nottingham in partnership with TCR Nottingham (see *Chapter 3*). Following pilot funding from the Medical Research Council, a network of collaborating GP investigators was developed.[65,66] The trial was co-ordinated 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[67] to invite trial participation. To maintain data security, each patient's NHS number was encrypted (using the AES-256 encryption standard), with the NHS number itself as the unique encryption key to prevent 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, record baseline data and carry out a *H. pylori* breath test.

Participants

Men and women aged ≥ 60 years, who were taking aspirin ≤ 325 mg 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 (see *Report Supplementary Material 2*). People concurrently using other antiplatelet agents were allowed to enter the study, but prescription of PPIs, H2RAs or NSAIDs were exclusion criteria (see *Report Supplementary Material 3*).

Helicobacter pylori status was determined using the *Helicobacter* test INFAI,[68] conducted by trained research nurses during the patient's screening visit (see *Report Supplementary Material 4*). 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 (NCTU) using a validated, web-based system with separate sequences for each regional centre using permuted blocks of randomly varying size. Block sizes were selected from 2, 4 and 6 using the ralloc function in Stata® (StataCorp LP, College Station, TX, USA). The participants were assigned to the intervention by the NCTU data manger, and the allocation (Group A vs. Group B, blinded as to which was active and which control) was accessed by the screening nurse through the web-based system after the patient had consented for randomisation. The participants, their GPs and healthcare 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 NCTU retained the key to unmask the data throughout the trial. Individual unmasked data could be supplied by the trial pharmacist for safety reasons.

Interventions

Active treatment consisted of twice daily lansoprazole 30 mg, clarithromycin 500 mg and metronidazole 400 mg, taken for 1 week.[69] Control patients received placebos corresponding to each of the active treatments to be taken twice daily for 1 week. Active and placebo treatments were stored and dispensed from a dedicated pharmacy unit (see *Report Supplementary Material 5*) maintained by the co-ordinating 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 (AEs).

Follow-up

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 (30 June 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 5 February 2019 and 6 September 2019 to be done at home[70] to assess the antibacterial efficacy of the eradication treatment.

Identification of outcomes

Events during follow-up were identified from searches of nationally held HES [www.hesonline.nhs.uk/Ease/servlet/contentserver?Siteid=1937&categoryid=214 (accessed 7 February 2011)] and Office for National Statistics (ONS) mortality data [www.statistics.gov.uk/statbase/Product.asp?Vlnk=14409 (accessed 7 February 2011)], from the locally held GP databases (Read codes) [https://digital.nhs.uk/services/terminology-and-classifications/read-codes (accessed 6 June 2023)], and from patient and GP spontaneous reports (see *Report Supplementary Material 1*). 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. A complete listing of data from HES, supplied annually, covered the period from trial start (14 September 2012) to finish (30 June 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 that were used to determine secondary outcomes using primary care data were censored from the date of their last upload.

The adjudication process

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 (see *Report Supplementary Material 6*). Whenever the trial management group received information (from any source) alerting them to the possibility of a potential case for adjudication, they assessed whether it could plausibly be a primary outcome, using a very liberal and inclusive

approach. For a patient to be deemed as having been hospitalised, there had to be a relevant HES record indicating hospital referral and contact. This included patients who were evaluated as outpatients and discharged on the same day. Those that were inpatients for other reasons who were transferred to the gastroenterology service were also included.

For all episodes that could be a primary end point, an information pack was prepared with a standardized case summary report form and photocopies of all relevant redacted information from GP data files and hospital notes. These were passed in batches of 10–20 to the committee who were asked to make a consensual assessment of bleed severity, mode of presentation, presence or absence of signs of bleeding such as shock, tachycardia, drop in haemoglobin, the detected lesion, and the presence or absence of stigmata of recent haemorrhage and decide if the episode met criteria for a primary outcome. The committee could ask for additional information. Their evaluations were guided by the criteria used in the TARGET study,[71] but they were asked to use discretion and inference where appropriate.

Outcomes

Primary outcome

The primary outcome was time to the first episode of hospitalisation or death due to definite or probable peptic ulcer bleeding, as determined by the adjudication committee. The initial published protocol omitted to include death due to peptic ulcer bleed, noted while planning the statistical analysis after the trial had finished, but before the code was broken. Both hospitalisation and death categories were then explicitly included in the primary outcome in the planned analysis, no pre-hospitalisation peptic ulcer deaths.

Secondary outcomes

Gastroduodenal ulcer bleeds

This comprised time to first episode of hospitalisation or death due to gastric or duodenal ulcer bleeding (oesophageal ulcer bleeds excluded).

All other causes of major or clinically significant gastrointestinal bleeding

This comprised all major and clinically evident bleeding episodes that were not adjudicated as a primary end point. Major bleeds were clinically evident events accompanied by definite vital signs of bleeding, need for blood transfusion or a fall in haemoglobin of 2 g/dl or haematocrit of 6%. Bleeds that were clinically evident but not accompanied by these signs of bleeding were classified as 'less severe', clinically significant bleeds (see details in *Report Supplementary Material 6*).

Detected uncomplicated ulcers

Uncomplicated ulcers were those detected in the absence of major or less-severe clinically significant bleeding.

Dyspepsia

The time to first GP consultation for dyspepsia recorded in clinical records, and the number of GP consultations for dyspepsia, during trial follow-up.

Antiulcer/dyspepsia medication

This was time to first prescription of a PPI, H2RA, antacid or alginate during follow-up in GP records, regardless of whether it was a single prescription or the start of a chronic course of treatment. To assess 6-monthly prevalence of prescribing at any time point, we also calculated the number of subjects with a prescription in the previous 90 days.

Withdrawal of prescription of aspirin

We defined withdrawal of aspirin as there being 90 days without a prescription, regardless of whether withdrawal was permanent or followed by reinstatement of aspirin prescription based on GP prescribing records. To assess prevalence of prescribing at any time point, we also calculated the number of subjects with a prescription in the previous 90 days.

Time to first thrombotic cardiovascular outcome

Cardiovascular events were based on unadjudicated (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) ICD-10 codes recorded in HES or ONS: for MI, cerebrovascular accident (CVA) and sudden cardiac deaths (see *Report Supplementary Material 7*).

The following ICD-10 codes were used (see *Report Supplementary Material 7*):

- MI: I21 (including all subcategories I21.0–I21.4 and I21.9)
- CVA: I63 (all subcategories I63.0–I63.9)
- Sudden cardiac death: I46.1

Any one of the individual event types would constitute a thrombotic CV outcome. Each individual event type was also recorded separately. Some participants had more than one type of event. The first to occur constituted the outcome event.

Adverse events and death

Because patients only received 1 week of routinely used treatment, and in conjunction with Medicines and Healthcare products Regulatory Agency (MHRA), we set a 4-week window for the routine collection of suspected treatment-related AEs reported by patients on the report form included 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

The final statistical analysis plan (SAP), finalised prior to code break, is shown as *Report Supplementary Material 8*. 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 HR and 95% CI comparing treatment groups for the primary end point. 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.[72] 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 (NNT) to avoid one ulcer bleed was calculated using the time to event method of Altman *et al.*[73]

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 group and age interaction was assessed for significance using a likelihood ratio test. A Fine–Gray model was used to estimate the subdistribution HR for the association between eradication treatment and the primary outcome accounting for the competing risk of death.[74] A per-protocol analysis was carried out restricted to patients who reported that they had taken eight or more doses of trial medication or placebo. This analysis has the implicit assumption that the two groups remain comparable after excluding patients, so can be susceptible to selection bias if this is not the case.

The secondary outcomes based on time to event were analysed using Cox proportional hazards models. The numbers of GP-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 PPI medication or other antiulcer/dyspepsia medication (H2RA, antacid, alginate) during follow-up were compared between treatment groups using Cox proportional hazards models. The point prevalence of prescriptions for aspirin, PPIs and H2RAs were estimated at 6-monthly time points throughout the study follow-up period. To assess the effect of changes in medications, we fitted a Cox model adjusting the primary outcome for the time-varying exposures to all the above

medications. Prescription dates within 90 days were defined as a continuous exposure with no gap. A model was then fitted with an interaction between aspirin use and eradication therapy, to assess the effect of eradication while patients were recorded as taking aspirin.

Powering the study

The data used to inform power calculations for HEAT have been published elsewhere[65] (see also *Report Supplementary Material 9*). Based on an average of the rates of ulcer bleeding in control patients in RCTs and observational studies, we assumed a rate of 0.16% pa in patients not taking aspirin. If aspirin increases the bleeding rate 2.5-fold, we would predict an ulcer bleeding rate in patients ≥ 60 years old on aspirin of 0.4% pa (all participants, *H. pylori* positive and negative). We assumed approximately 25% of patients would have a positive *H. pylori* breath test (as in our pilot study) and that infection would increase the risk of bleeding threefold (as in our pilot study). Based on these metrics, we postulated an ulcer bleeding rate of 2.67 per 1000 pa in the 75% of patients were on aspirin and naturally *H. pylori* negative, 8 per 1000 in the 25% who were *H. pylori* positive, and a halving to 4 per 1000 pa in the intervention group (plausibly still 50% higher than in naturally *H. pylori* patients).

To detect a HR of 0.5 comparing the intervention with the control group, with a 5% two-sided significance level and 90% power, a total of 87 primary outcome events would be required, with 145,000 person-years of exposure. Due to a smaller-than-expected proportion of patients that were *H. pylori* positive and a lower primary end-point 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 end points had occurred.

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Chapter 5 *Helicobacter* Eradication Aspirin Trial Results

Recruitment

The trial was conducted in 1208 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.

About 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 from 1055 practices (median 4 patients per practice, range 1–33 patients), with 5352 patients in the ITT population (*Figure 1*).

The overall profile of cumulative recruitment is shown in *Figure 2*.

Details of recruitment processes and challenges with a listing of participating GPs, primary care trusts and Clinical Commissioning Groups (CCGs) are detailed in Stevenson *et al.*[66]

Baseline characteristics

There were 2677 participants randomised to the eradication group and 2675 to the control group in the ITT analysis (see *Figure 1*, *Table 1*).

Overall, the mean age at consent was 73.6 [standard deviation (SD) 6.9] years, and 72.8% of participants were male. Treatment groups were well balanced for ulcer-risk factors and demographic features (see *Table 1*).

Comorbidities

Coronary heart disease was the most common comorbidity among aspirin indications, followed by diabetes mellitus and a history of stroke or TIA (*Table 2*).

Fewer than 2% had a history of peptic ulcer. The commonest risk factor for peptic ulceration was a past history of smoking (52.8% of participants). Use of drugs capable of influencing ulcer development prescribed in the 90 days prior to the date of randomisation are shown in *Table 2*. Ten per cent of patients had been prescribed nitrates in the 90 days before randomisation.

Adherence to trial treatments

Similar numbers in each group (eradication treatment group: 15.6%, control group: 16.1%) recorded no treatment doses in their diaries or failed to return them (see *Table 3*).

More of those in the control group (79.7%) took all 14 doses compared to those taking active eradication treatment (73.4%), and more had taken 8 or more doses (83.2% vs. 80.1%, $p = 0.003$). This difference arose because there were more participants in the eradication group who started treatment but did not complete the full course (*Figure 3*).

For the purpose of analysis, participants who reported taking at least 8 doses were pragmatically regarded as the per-protocol group.

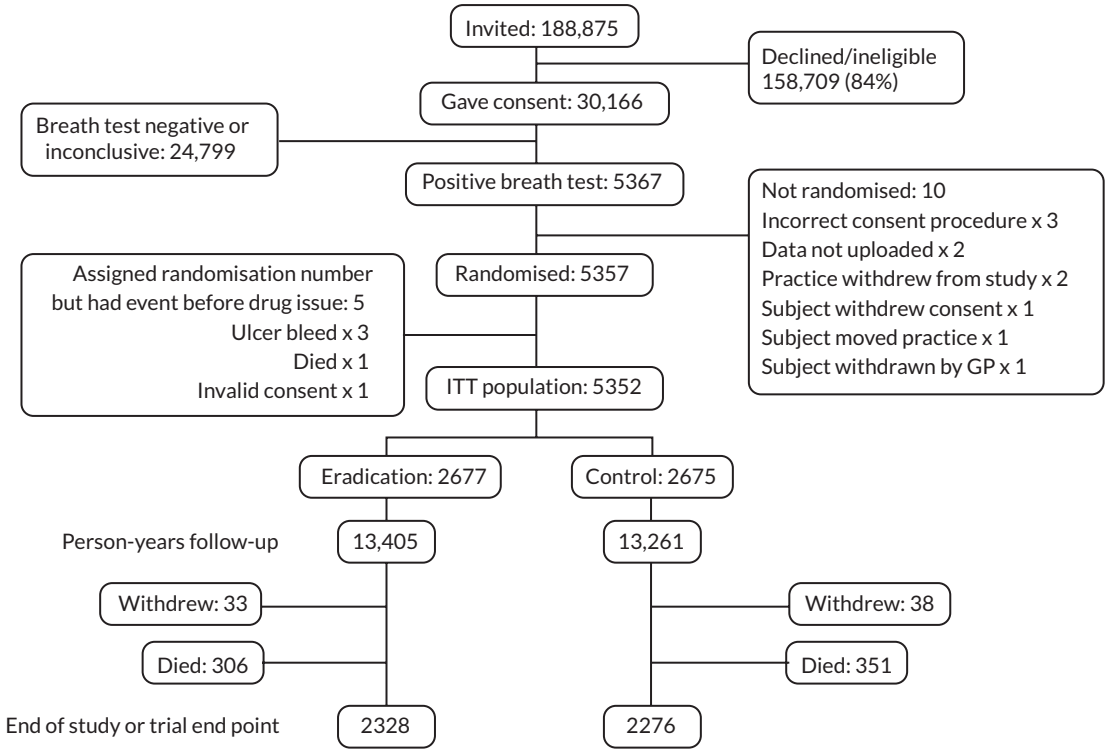


FIGURE 1 Trial profile (Consolidated Standards of Reporting Trials diagram). Note: All patients who received the study intervention drugs or placebo were in the ITT group (n = 5352) and in the analysis group. Patients were followed up until the earliest of death date, primary outcome date, end-of-study date or date of withdrawal.

FIGURE 2 Recruitment and randomisation.

Follow-up

Randomised patients were followed up for a total of 26,668 person-years [median 5.0 years interquartile range (IQR) 3.9–6.4] until they either withdrew consent, died or reached the end of the study (30 June 2020).

TABLE 1 Baseline characteristics

	Eradication group	Control group
	N = 2677	*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%)
Mean age at randomisation (SD)	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%)
Drinks alcohol		
No	731 (27.3%)	768 (28.7%)
Yes	1830 (68.4%)	1810 (67.7%)
Missing	116 (4.3%)	97 (3.6%)
Alcohol units per week (median, IQR)[a]	8.0 (3.0–16.0)	8.0 (3.0–16.0)
Mean body mass index (SD)	28.2 (4.8)	28.3 (4.9)
IMD decile (median, IQR)	7.0 (4.0–9.0)	7.0 (4.0–9.0)

a In those reporting drinking alcohol.
IMD, Index of Multiple Deprivation.

TABLE 2 Comorbidities and prescribed medications in randomised patients at baseline

	Eradication group	Control group
	N = 2677	*N* = 2675
Comorbidities recorded before baseline:		
Coronary heart disease	1285 (48.0%)	1347 (50.4%)
Stroke/TIA	355 (13.3%)	365 (13.6%)
Diabetes	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 90 days before randomisation:		
Antacids	24 (0.9%)	17 (0.6%)
Antidepressants (SSRIs/venlafaxine)	85 (3.2%)	65 (2.4%)
Corticosteroids	49 (1.8%)	45 (1.7%)
Nitrates	274 (10.2%)	266 (9.9%)
PPI[a]	72 (2.7%)	61 (2.3%)
H2RA[a]	4 (0.1%)	5 (0.2%)
NSAIDs[a]	47 (1.8%)	43 (1.6%)
COX-2 inhibitors	2 (0.1%)	2 (0.1%)
Other antiplatelet or anticoagulant[b]	20 (0.7%)	18 (0.7%)

COX-2, cyclo-oxygenase 2; SSRI, selective serotonin reuptake inhibitor.
a Exclusion criterion at baseline visit.
b Included warfarin (*n* = 17), dipyridamole (*n* = 18), and ticagrelor (*n* = 3).

End-of-study *Helicobacter pylori* status

In the 10% sample of patients with a retest of *H. pylori* status at a median of 3.95 (IQR 2.76–5.28) years after randomisation, 146 in the eradication group (90.7%) had a negative breath test versus 41 (24.0%) in the control group ($p < 0.001$). There was no relationship between the number of treatment doses taken and the final *H. pylori* status.

Adjudications

In total, 596 events from 587 participants were sent to the adjudication committee, of which 141 cases were adjudicated to involve major or clinically significant GI bleeding. In total, 44 cases were adjudicated to be cases of definite or probable peptic ulcer bleeding, based on evaluation of clinical presentation and endoscopic findings as detailed in the adjudication committee charter (see *Report Supplementary Material 6*). These included three cases, in which the clinical presentation was inferred from laboratory results, and there were stigmata of recent haemorrhage at endoscopy.

TABLE 3 Adherence to trial medications

	Eradication	Control
	N = 2677	*N* = 2675
Number of times took treatment		
0	418 (15.6%)	432 (16.1%)
1	8 (0.3%)	2 (0.1%)
2	9 (0.3%)	3 (0.1%)
3	19 (0.7%)	1 (0.0%)
4	26 (1.0%)	5 (0.2%)
5	15 (0.6%)	2 (0.1%)
6	29 (1.1%)	2 (0.1%)
7	10 (0.4%)	2 (0.1%)
8	27 (1.0%)	1 (0.0%)
9	11 (0.4%)	3 (0.1%)
10	12 (0.4%)	6 (0.2%)
11	9 (0.3%)	1 (0.0%)
12	27 (1.0%)	17 (0.6%)
13	91 (3.4%)	65 (2.4%)
14	1966 (73.4%)	2133 (79.7%)

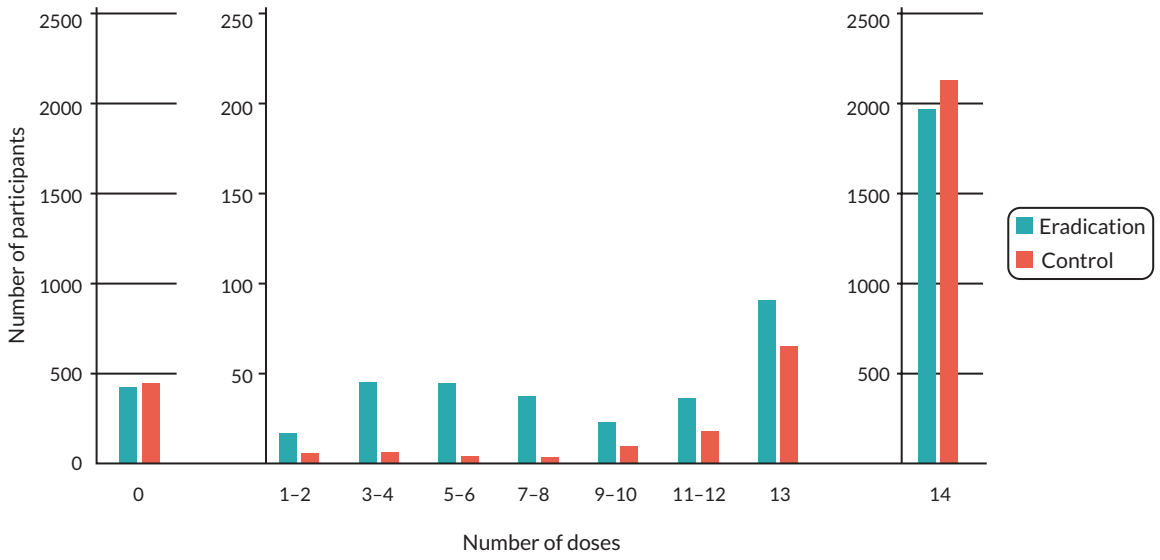


FIGURE 3 Treatment adherence. Outer panels 10× magnification scale compared to inner panel.

Primary outcome

Of the 44 episodes adjudicated to be definite or probable peptic ulcer bleeds, there were 18 in the eradication group and 26 in the control group (*Table 4*) during whole follow-up period with overall incidence rates of 1.34 per 1000 person-years and 1.96 per 1000 person-years, respectively.

The Kaplan–Meier curves for the two treatment groups deviate early and remain separate throughout the follow-up period, suggesting a possible survival advantage for the eradication group, particularly in the first 1–2 years (*Figure 4*). However, the numbers involved are small, and an unselective analysis over the full follow-up period adjusted for study centre showed that the HR for the eradication group versus control group of 0.69 (95% CI 0.38 to 1.25) was not statistically significant (p = 0.218, *Table 5*).

TABLE 4 Incidence of primary outcome (hospitalisation or death due to peptic ulcer bleeding) during whole follow-up period

	Person time (Years)	Events	Rate per 1000	95% CI
ITT population:				
Eradication group	13,405.6	18	1.34	0.85–2.13
Control group	13,263.0	26	1.96	1.33–2.88
Total	26,668.5	44		
Per protocol population:				
Eradication group	10,843.7	12	1.11	0.63
Control group	11,185.4	22	1.97	1.30
Total	22,029.2	34		

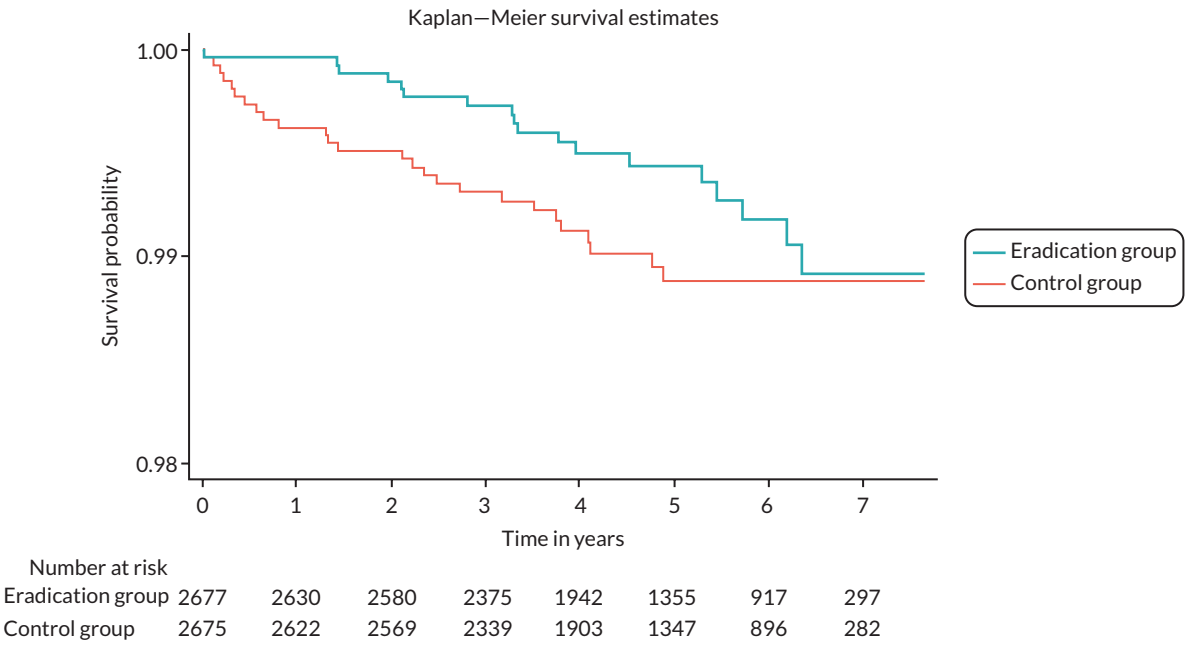


FIGURE 4 Primary outcome: Kaplan–Meier survival curves.

Schoenfeld analysis revealed a significant departure from the proportional hazards assumption of the Cox model (p = 0.0068, see *Table 5*). This time-dependent departure from the proportional hazards assumption was associated with a marked difference in hazard rates between the treatment groups early in the study follow-up after randomisation, but not later as shown in the Kaplan–Meier survival curve (see *Figure 4*) and illustrated by log minus log plots of the data (*Figure 5*).

Split time analyses

Accordingly, as mandated by the study protocol and SAP rules for dealing with a departure from proportional hazards assumptions, we fitted a single Cox model with time split in the data at the median of 2.5 years' follow-up. Two and a half years was selected prior to the unblinding of the data as the time point with equal numbers of events and follow-up in both periods. Similar numbers of events in the first and second time periods minimised loss of statistical power. This resulted in the Cox proportional hazards assumptions being met (p = 0.54 for the overall model). There were a total of 23 episodes of ulcer bleeding adjudicated as a primary outcome in the first 2.5 years after randomisation, 6 in the eradication group and 17 in controls, and a total of 21 after 2.5 years, with 12 in the eradication group and 9 in controls.

TABLE 5 Primary outcome: HR over full follow-up period

ITT analysis adjusted for study centre	HR	95% CI		*p*-value
Randomisation group:				
Eradication vs. control	0.69	0.38	1.25	0.218
Study centre[a]				
Birmingham	0.64	0.23	1.78	0.39
Durham	0.86	0.36	2.06	0.74
Nottingham	1.00			
Oxford	0.90	0.35	2.35	0.83
Southampton	0.78	0.35	1.72	0.54

a Nottingham centre includes Belfast and Scotland.

Note
Test of proportional hazards assumption for randomisation group: p = 0.0068.

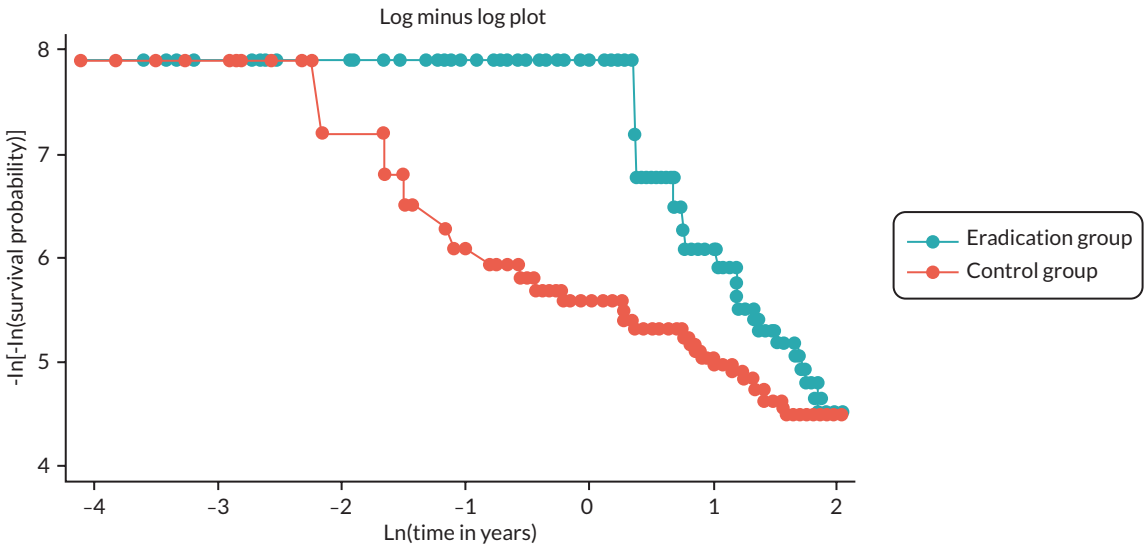


FIGURE 5 Log minus log curves for primary outcome.

The HR in the first 2.5 years was 0.35 (95% CI 0.14 to 0.89; p = 0.028, *Table 6*), with a rate of 0.92 (95% CI 0.41 to 2.04) per 1000 person-years in the eradication treatment group and 2.61 (95% CI 1.62 to 4.19) per 1000 person-years in the control group, giving an NNT of 238 (95% CI 184 to 1661). In the second follow-up period after 2.5 years, the rate in the eradication treatment group was 1.75 (95% CI 0.99 to 3.08) per 1000 person-years and 1.33 (95% CI 0.69 to 2.56) per 1000 person-years in the control group, with a HR of 1.31 (95% CI 0.55 to 3.11; p = 0.540, see *Table 6*). Results were similar after adjustment for age and sex (*Table 7*).

Per-protocol analysis

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 group, 15 in the control group), and a HR of 0.21 (95% CI 0.06 to 0.71; p = 0.013, *Table 8*).

TABLE 6 Primary outcome: HR over split follow-up periods

ITT analysis adjusted for study centre	HR	95% CI		*p*-value
First 2.5 years				
Eradication vs. control	0.35	0.14	0.89	0.028
2.5 years onwards				
Eradication vs. control	1.31	0.55	3.11	0.540
Test of proportional hazards assumption for randomisation groups: p = 0.54				

Note
Whole time analysis not shown: invalidated by violation of the proportional hazards assumptions.

TABLE 7 Primary outcome: event rates and HRs. Sensitivity analysis

Hospitalisation due to ulcer bleeding	Episodes	Rate/1000 person-years	HR (95% CI) Eradication vs. control: Adjusted for study centre as fixed effect	*p*-value	Adjusted for study centre, age and sex	*p*-value	Adjusted for study centre and time-varying prescribed medications[a]	*p*-value
< 2.5 years								
Control	17	2.61 (1.62 to 4.19)						
Eradication	6	0.92 (0.41 to 2.04)	0.35 (0.14 to 0.89)	0.028	0.36 (0.14 to 0.90)	0.030	0.33 (0.12 to 0.90)	0.03
> 2.5 years								
Control	9	1.33 (0.69 to 2.56)						
Eradication	12	1.75 (0.99 to 3.08)	1.31 (0.55 to 3.11)	0.540	1.33 (0.56 to 3.15)	0.521	1.05 (0.45 to 2.48)	0.91
Whole time[b]								
Control	26	1.96 (1.33 to 2.88)						
Eradication	18	1.34 (0.85 to 2.13)	0.69 (0.38 to 1.25)	0.218	0.69 (0.38 to 1.27)	0.235	0.62 (0.33 to 1.26)	0.14

a Based on 40 episodes (primary care component of end point censored for drug use data because of delayed upload).
b Invalid analysis because of violation of the proportional hazards assumptions. Included for context.

The first episode of ulcer bleeding adjudicated as a primary outcome in the per-protocol eradication treatment group occurred at 525 days after randomisation versus 6 days for controls.

Competing risks analysis

A Fine–Gray model used to adjust for the competing risk of death showed that the difference between the eradication group and the control group (*Figure 6*) remained significant in the first 2.5 years (*Table 9*). The subdistribution HR within 2.5 years was 0.35 [95% CI 0.14 to 0.89; $p = 0.028$, and 1.32 (0.56 to 3.14; $p = 0.528$)] subsequently.

TABLE 8 Primary outcome: HR over split follow-up periods

Per-protocol analysis adjusted for study centre	HR	95% CI		*p*-value
First 2.5 years				
Eradication vs. control group	0.22	0.06	0.77	0.018
2.5 years onwards				
Eradication vs. control group	1.15	0.44	2.99	0.77

Note
This includes total of 34 primary outcomes occurring in participants taking at least eight doses of eradication treatment.

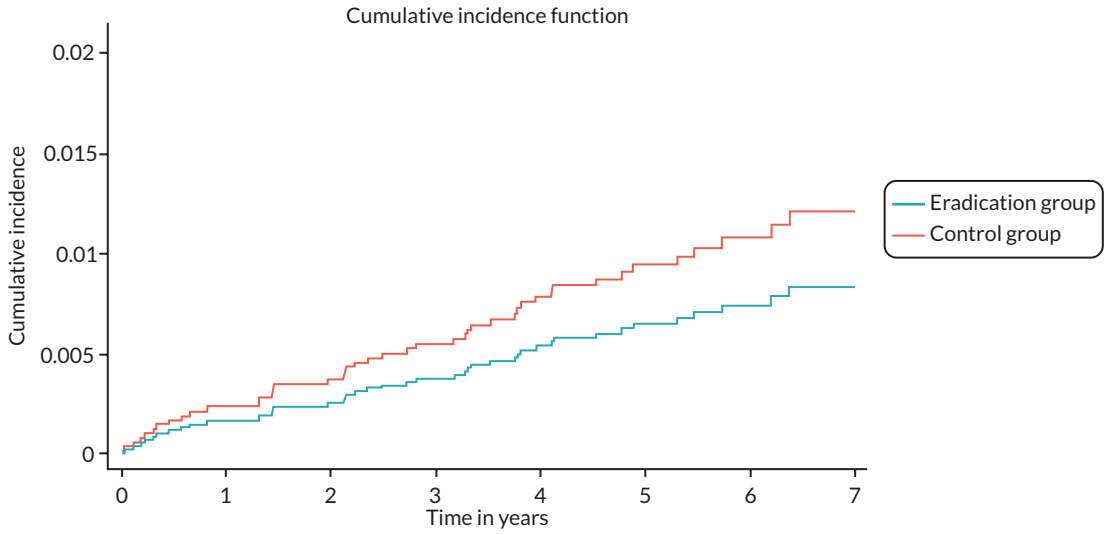


FIGURE 6 Primary outcome: cumulative incidence in competing risks model.

TABLE 9 Primary outcome: subdistribution HR over split follow-up periods

	Subdistribution HR	95% CI		*p*-value
First 2.5 years				
Eradication vs. control	0.35	0.14	0.89	0.028
2.5 years onwards				
Eradication vs. control	1.32	0.56	3.14	0.528

TABLE 10 Ulcer site associated with primary outcome

	All	Eradication	Control
Oesophageal	7 (15.9%)	5 (29.4%)	< 5
Gastric	22 (50%)	6 (35.3%)	16 (59.3%)
Duodenal	14 (31.8%)	6 (35.3%)	8 (29.6%)
All	43[a]	17	26

a One subject frank major haematemesis, too unwell for endoscopy, no better cause than ulcer (TARGET category 5A).

Ulcer site

A gastric ulcer was the underlying lesion in 22 (51%) of patients experiencing a primary outcome, with 16 in the control group and 6 in the eradication treatment group (*Table 10*).

Secondary outcomes

Statistical approach

Data that were based on time to event (gastroduodenal ulcer bleeding, all other causes of GI bleeding, uncomplicated ulcers, onset of dyspepsia, changes in drug prescription and CV outcomes) were analysed by Cox proportional hazards in the same way as the primary outcome. If Schoenfeld testing indicated a significant departure from proportional hazards assumptions, this was done on the same split time periods as used for the primary outcome. Otherwise, a simple Cox proportional hazards approach was applied to the whole follow-up period. Results are tabulated in *Table 11* and then presented for each outcome, separately.

Gastroduodenal ulcer bleeding

Kaplan–Meier survival curves for the secondary outcome restricted to hospitalisation due to gastric or duodenal ulcer bleeding showed a pattern similar to the primary outcome (*Figure 7*). This is not surprising given that this parameter is a subset of the primary outcome analysis.

In an analysis adjusted for study centre, covering the whole follow-up period, the Cox proportional hazards assumption was not met (Schoenfeld test $p = 0.0115$, *Table 12*), and a split time analysis was employed. There was a significant difference in gastroduodenal ulcer bleeding between treatment groups (HR 0.31, 95% CI 0.11 to 0.85; $p = 0.023$) over the first 2.5 years but not thereafter (HR 1.10, 95% CI 0.43 to 2.86; $p = 0.84$, *Table 13*).

Other secondary outcomes

In contrast to ulcer bleeding, Schoenfeld analysis showed no violation of proportional hazards assumptions for the other time-dependent measures (see *Table 11*), and these were analysed for the whole unsplit follow-up period.

Other causes of gastrointestinal bleeding

There were 97 cases of clinically significant GI bleeding, not due to peptic ulceration (*Figure 8*).

The commonest sources were diverticular disease (20), colorectal cancer (8), haemorrhoids (8), colonic polyps (7) and Mallory–Weiss tears (6). There was no significant difference between the two treatment groups (HR 1.10, 95% CI 0.74 to 1.64; $p = 0.64$) (*Table 14*).

Uncomplicated ulcers

Uncomplicated ulcers were found in 133 participants (67 in eradication group, 66 in control group) (*Figure 9*).

There was no significant difference between the treatment groups (HR 1.01, 95% CI 0.72 to 1.42; $p = 0.966$, *Table 15*).

TABLE 11 Secondary outcomes: events and HRs

Outcome	No. of events		Proportional hazards assumption	Eradication vs. control:			
				Main analysis[a]		Secondary analysis[b]	
	Eradication	Control	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gastroduodenal ulcer bleeding	14	24	0.0115[d]				
< 2.5 years	5	16		0.31 (0.11 to 0.85)	0.023	0.32 (0.12 to 0.86)	0.025
≥ 2.5 years	9	8		1.10 (0.43 to 2.86)	0.84	1.12 (0.43 to 2.90)	0.82
Other clinically significant non-ulcer causes of GI bleeding[c]	51	46	0.42[e]	1.10 (0.74 to 1.64)	0.635	1.11 (0.74 to 1.65)	0.61
Detected uncomplicated ulcers	67	66	0.57[e]	1.01 (0.72 to 1.42)	0.97	1.01 (0.72 to 1.42)	0.96
GP-recorded dyspepsia[f]	68	66	0.660	1.03 (0.74 to 1.45)	0.85	1.05 (0.70 to 1.55)	0.82
Number of dyspepsia consultations[g]	97	93	NA	1.04 (0.70 to 1.54)	0.85		
One or more prescriptions for							
PPI	1011	947	0.285[e]	1.09 (1.00 to 1.19)	0.049	1.09 (1.00 to 1.19)	0.048
H2RA	101	87	0.20[e]	1.16 (0.87 to 1.55)	0.30	1.17 (0.88 to 1.56)	0.28
Antacids	106	105	0.090[e]	1.02 (0.78 to 1.33)	0.91	1.02 (0.78 to 1.34)	0.89
NSAIDs	468	406	0.82[e]	1.17 (1.02 to 1.33)	0.022	1.16 (1.02 to 1.33)	0.025
Aspirin prescription stopped[h]	1150	1182	0.98[e]	0.98 (0.91 to 1.07)	0.71	0.99 (0.91 to 1.07)	0.73
CV outcomes	149	169	0.20[e]	0.87 (0.70 to 1.09)	0.23	0.88 (0.71 to 1.10)	0.27

a Adjusted for study centre as fixed effect.
b Adjusted for study centre, age and sex.
c Cause of hospitalisation.
d Proportional hazards assumptions violated: results are for first 2.5 years of follow-up.
e Proportional hazards assumptions valid: results are for whole follow-up.
f Rate ratio from negative binomial model.
g Negative binomial model.
h Missed at least 90 consecutive days of prescription.

Time to dyspepsia consultation in primary care

A small number of participants (134) were recorded as consulting their GP because of dyspepsia during follow-up: 68 (2.7%) in the eradication group and 66 (2.6%) in controls (*Table 16*). Schoenfeld analysis supported the proportional hazards assumptions ($p = 0.660$), so all follow-up data were used for a Cox proportional hazards analysis for the whole unsplit data set. There were no differences in the time from randomisation to a first dyspepsia consultation (*Figure 10*).

Number of dyspepsia consultations

Most of the participants who developed dyspepsia had one or two consultations during follow-up (*Table 17*).

Differences in this non-time-dependent parameter between the eradication group and controls were assessed as a rate ratio in a negative binomial model (see *Table 17*). There was no difference in the consultation rate between the two groups (rate ratio 1.04, 0.70 to 1.54; $p = 0.85$) (*Table 18*).

Changes in drug prescription during follow-up

During the lifetime of this study, there were changing recommendations on prescribing, including more widespread use of PPIs and other antisecretory drugs' interest in possible value of aspirin in cancer prevention and a questioning of its

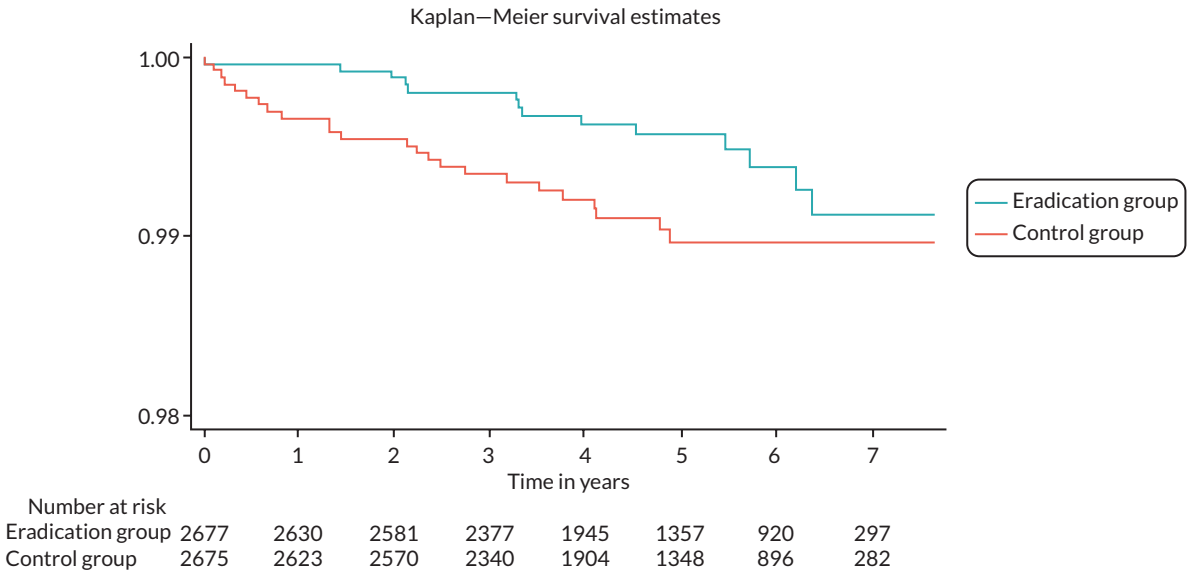


FIGURE 7 Gastroduodenal ulcer bleeding: Kaplan–Meier survival curves.

TABLE 12 Gastroduodenal ulcer bleeding (unsplit follow-up time)

	HR	95% CI		*p*-value
Randomisation group				
Eradication vs. control arm	0.58	0.30	1.12	0.103
Study centre[a]				
Birmingham	0.65	0.21	2.05	0.47
Durham	0.96	0.37	2.49	0.94
Nottingham	1.00			
Oxford	1.15	0.42	3.10	0.79
Southampton	0.90	0.38	2.13	0.81

a Nottingham centre includes Belfast and Scotland.

Note
Test of proportional hazards assumption for randomisation group: $p = 0.0115$.

TABLE 13 Gastroduodenal ulcer bleeding: HR over split follow-up periods

ITT analysis	HR	95% CI		*p*-value
First 2.5 years				
Eradication vs. control arm	0.31	0.11	0.85	0.023
2.5 years onwards				
Eradication vs. control group	1.10	0.43	2.86	0.837

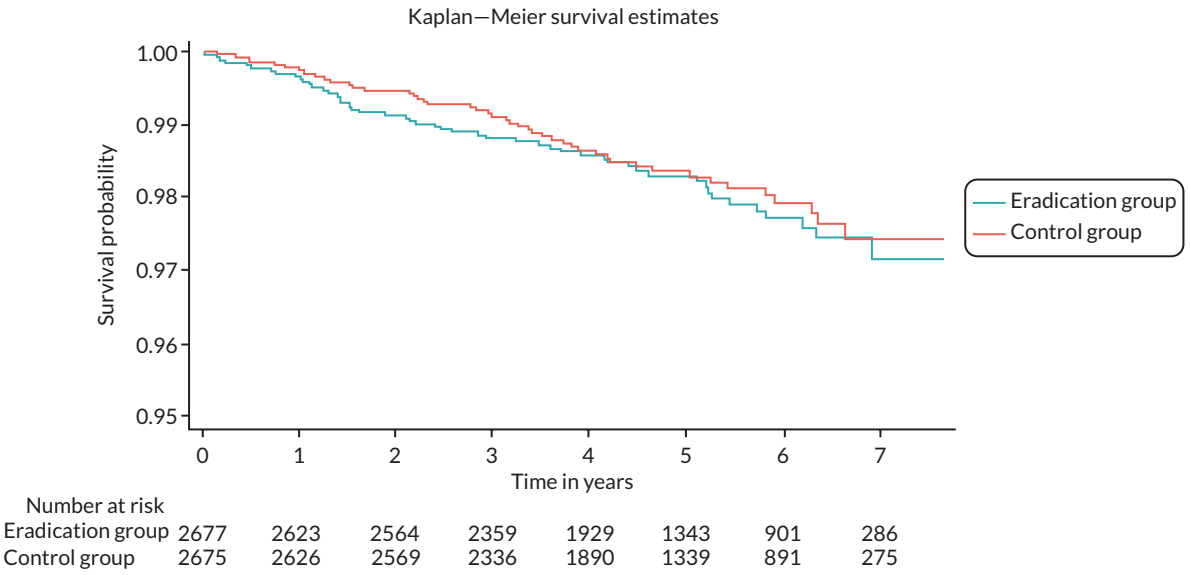


FIGURE 8 Other causes of GI bleeding: Kaplan–Meier survival curves.

TABLE 14 Other causes of GI bleeding

	HR	95% CI		*p*-value
Randomisation group				
Eradication group vs. controls	1.10	0.74	1.64	0.634
Study centre[a]				
Birmingham	0.33	0.15	0.74	0.01
Durham	0.82	0.48	1.42	0.48
Nottingham	1.00			
Oxford	0.51	0.25	1.05	0.07
Southampton	0.60	0.36	1.00	0.05

a Nottingham centre includes Belfast and Scotland.

Note
Test of proportional hazards assumption for randomisation group: $p = 0.42$.

use in primary prevention of CVD. We assessed overall point prevalence of prescribing at 6-monthly intervals as well as the time to starting gastroprotective drugs or stopping aspirin.

Point prevalence of prescribing

Prescriptions of aspirin fell progressively throughout the follow-up period (*Figure 11*).

After 2.5 years of follow-up, 82.4% of those in the eradication group and 82.6% in the control group were still taking aspirin. The point prevalence of PPI prescription increased progressively throughout follow-up: after 2.5 years, 12.5% and 12.3% of those in the eradication and control groups, respectively, were prescribed a PPI. Few participants were prescribed antacids or H2RAs.

TABLE 15 Uncomplicated ulcers: HRs for eradication group vs. control adjusted for study centre

	HR	95% CI		*p*-value
Randomisation group				
Eradication vs. control	1.01	0.72	1.42	0.966
Study centre[a]				
Birmingham	0.99	0.58	1.69	0.973
Durham	1.00	0.61	1.65	0.988
Nottingham	1.00			
Oxford	0.65	0.34	1.24	0.187
Southampton	0.95	0.60	1.49	0.814

a Nottingham centre includes Belfast and Scotland.

Note
Analysis excludes two people who had this outcome before randomisation date.

TABLE 16 Time to dyspepsia consultation

	HR	95% CI		*p*-value
Randomisation group				
Eradication vs. control	1.03	0.74	1.45	0.85
Study centre[a]				
Birmingham	1.10	0.66	1.83	0.72
Durham	0.97	0.59	1.59	0.89
Nottingham	1.00			
Oxford	0.80	0.44	1.48	0.48
Southampton	0.88	0.55	1.40	0.59

a Nottingham centre includes Belfast and Scotland.

Note
Test of proportional hazards assumption for randomisation group: $p = 0.660$.

Stopping aspirin

Approximately half of the HEAT participants had stopped aspirin by the end of the study (*Figure 12*). This is more than the point prevalence over the same time frame, suggesting that for the first-use data, some of the gap in prescribing was temporary.

Starting gastroprotective drugs or non-steroidal anti-inflammatory drugs

Schoenfeld analysis supported proportional hazards assumptions, and the data were analysed for the whole of the study period. More than half of the participants had received a PPI by the end of the study period. Time to first gastroprotective drug and NSAID use was reduced in the eradication group (*Figure 13*).

As with gaps in aspirin prescribing, the incidence was higher than the prevalence, suggesting some of the exposure was for short-term use.

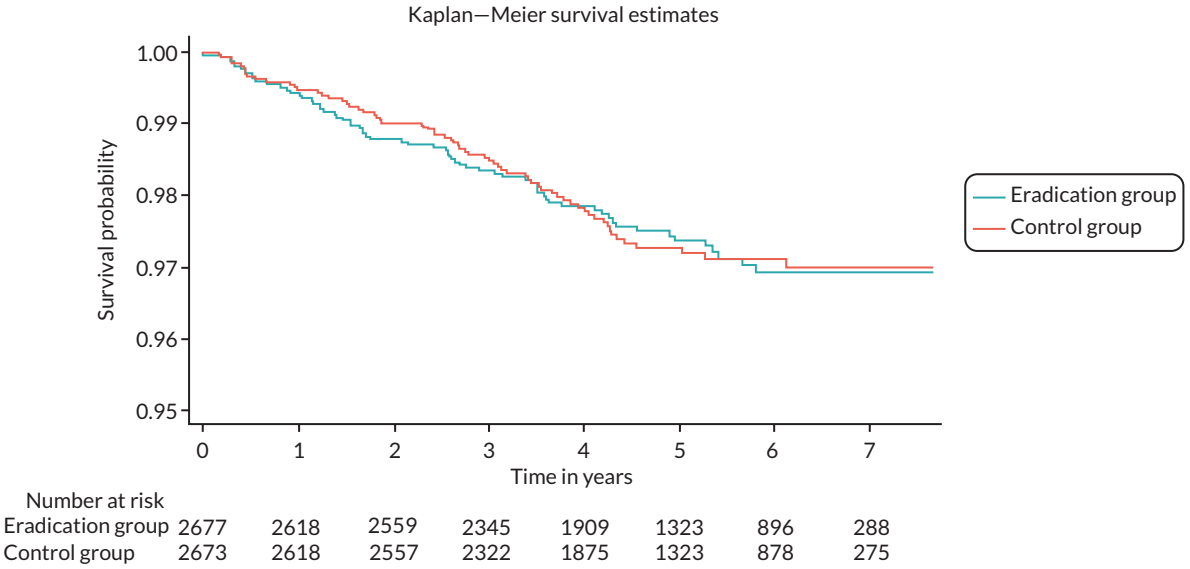


FIGURE 9 Uncomplicated ulcers: Kaplan–Meier survival curves.

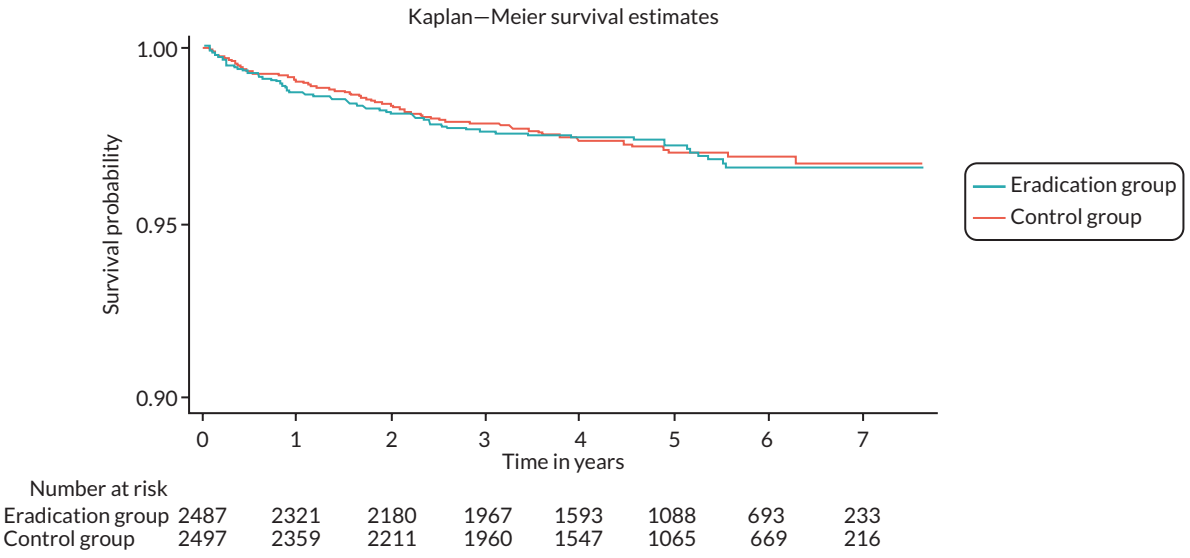


FIGURE 10 Time to dyspepsia consultation: Kaplan–Meier survival curves.

TABLE 17 Number of primary care dyspepsia consultations during follow-up

	Eradication group	Control group
	N = 2487	*N* = 2498
0	2419 (97.3%)	2431 (97.4%)
1	47 (1.9%)	51 (2.0%)
2	16 (0.6%)	9 (0.4%)
3	3 (0.1%)	2 (0.1%)
4	1 (0.0%)	2 (0.1%)
5	1 (0.0%)	2 (0.1%)

Note
Excludes 368 people with no relevant GP follow-up data.

TABLE 18 Primary care dyspepsia consultations during follow-up

	Rate ratio	95% CI		*p*-value
Randomisation group				
Eradication vs. control	1.04	0.70	1.54	0.85
Study centre[a]				
Birmingham	0.90	0.48	1.68	0.74
Durham	0.92	0.52	1.65	0.79
Nottingham	1.00			
Oxford	0.91	0.47	1.78	0.78
Southampton	0.96	0.57	1.63	0.88

a Nottingham centre includes Belfast and Scotland.

Note
Adjusted for study centre, from negative binomial regression model.

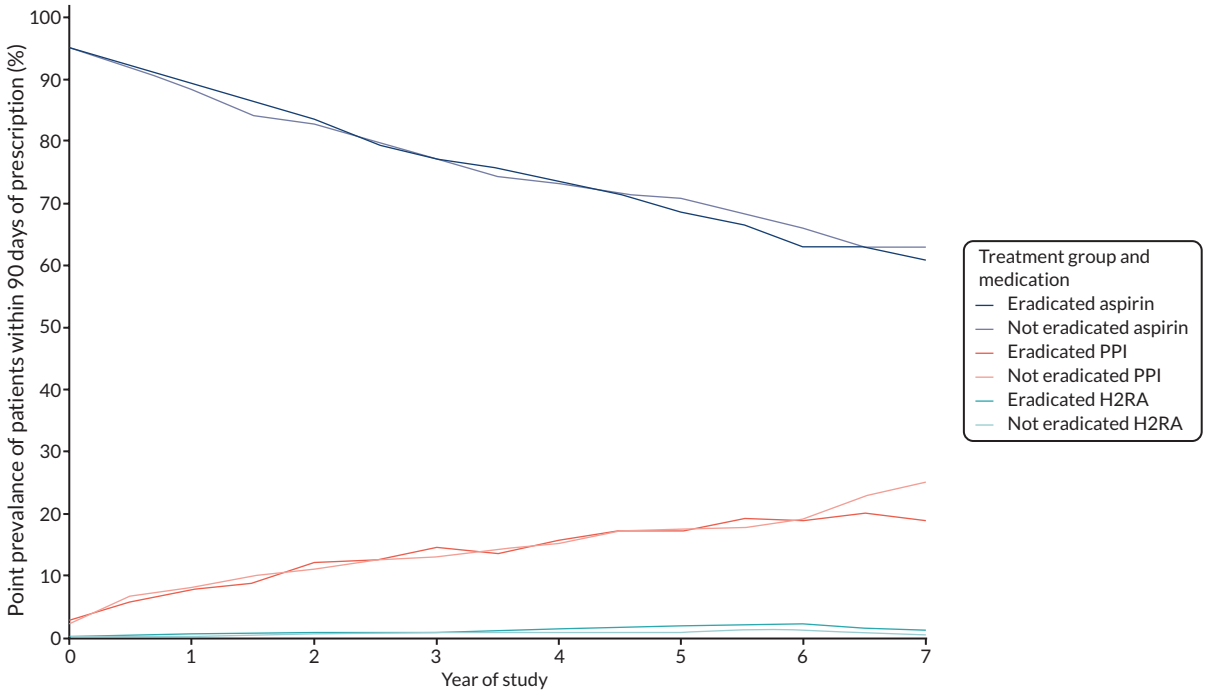


FIGURE 11 Changes in point prevalence of drug prescription. Per cent of participants with prescription in the previous 90 days, assessed at 6-monthly intervals.

Prescription of H2RAs and antacids also increased over follow-up, but at a lower level than for PPIs. Although NSAID use is discouraged for a number of reasons, including adverse interactions with aspirin, some 20% of participants had received NSAIDs by the end of the study, reflecting the influence of age on both CV and rheumatological conditions. Use of NSAIDs and PPIs were significantly associated with eradication (*Table 19*). Other drug associations were not significant.

Cardiovascular outcomes

Cardiovascular outcomes did not significantly differ between the eradication and control group (*Table 20*, *Figure 14*).

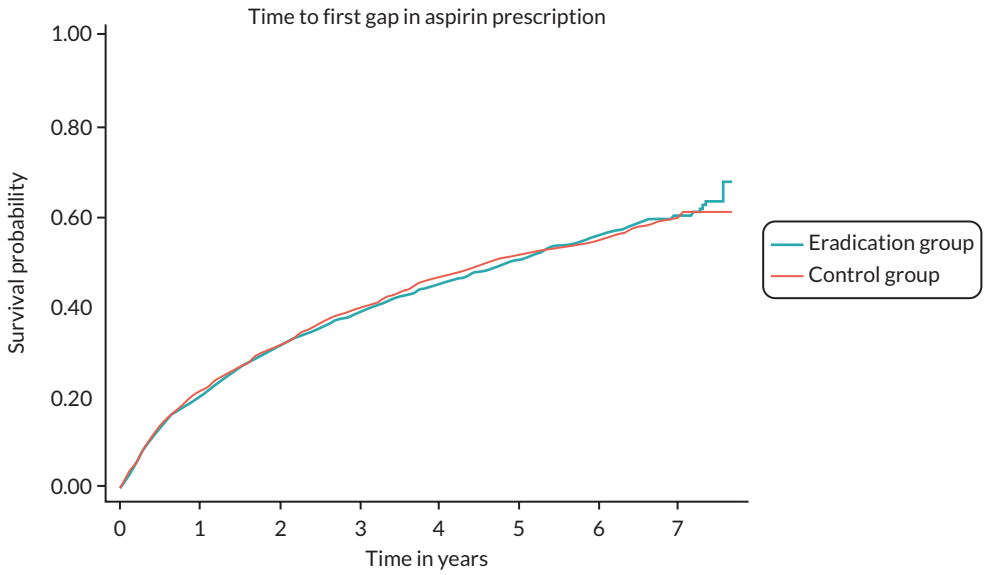


FIGURE 12 Kaplan–Meier curve of time to first gap in aspirin prescription.

Prescribing in participants with a primary outcome

Of the 44 patients with a primary outcome, 35 (79.5%) were still prescribed aspirin, 11 (25.0%) were prescribed a PPI and 2 (1 patient in each treatment group) were on an NSAID at the time of presentation. None of the patients hospitalised for peptic ulcer bleeding had taken non-aspirin antiplatelet or anticoagulant medication in the year prior to presentation.

There were too few primary outcome events to power an analysis restricted to patients only prescribed aspirin and not the other medications during follow-up, 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, 95% CI 0.12 to 0.90; $p = 0.03$, see *Table 7*). The addition of an interaction between current aspirin use and eradication therapy estimated an increase in the effect of eradication in current aspirin users during the first 2.5 years (HR 0.22, 95% CI 0.06 to 0.79), but not in the last 2.5 years (HR 1.27, 95% CI 0.44 to 3.67), although the latter has a larger uncertainty due to few events.

Possible drug influences on end-of-study breath tests

The unexpectedly high number of patients in the control group sample with a negative end-of-study breath test prompted exploratory analyses of antibiotic exposure as a possible cause of eradication or PPIs as a cause of a negative breath test. 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 versus 10 of 127 (8%) with a positive test. An alternative explanation is that home testing resulted in some false negative results.

Adverse events

There were 5293 reports of AEs (4006 in the eradication group, 1287 in the control group) in the 4 weeks from the start of trial treatment (*Table 21*).

This high frequency of AEs reflects the proactive collection via participant completed diaries. The pattern of reported AEs was similar to that already recognised for the drugs used. The most common were taste disturbance, diarrhoea and abdominal pain.

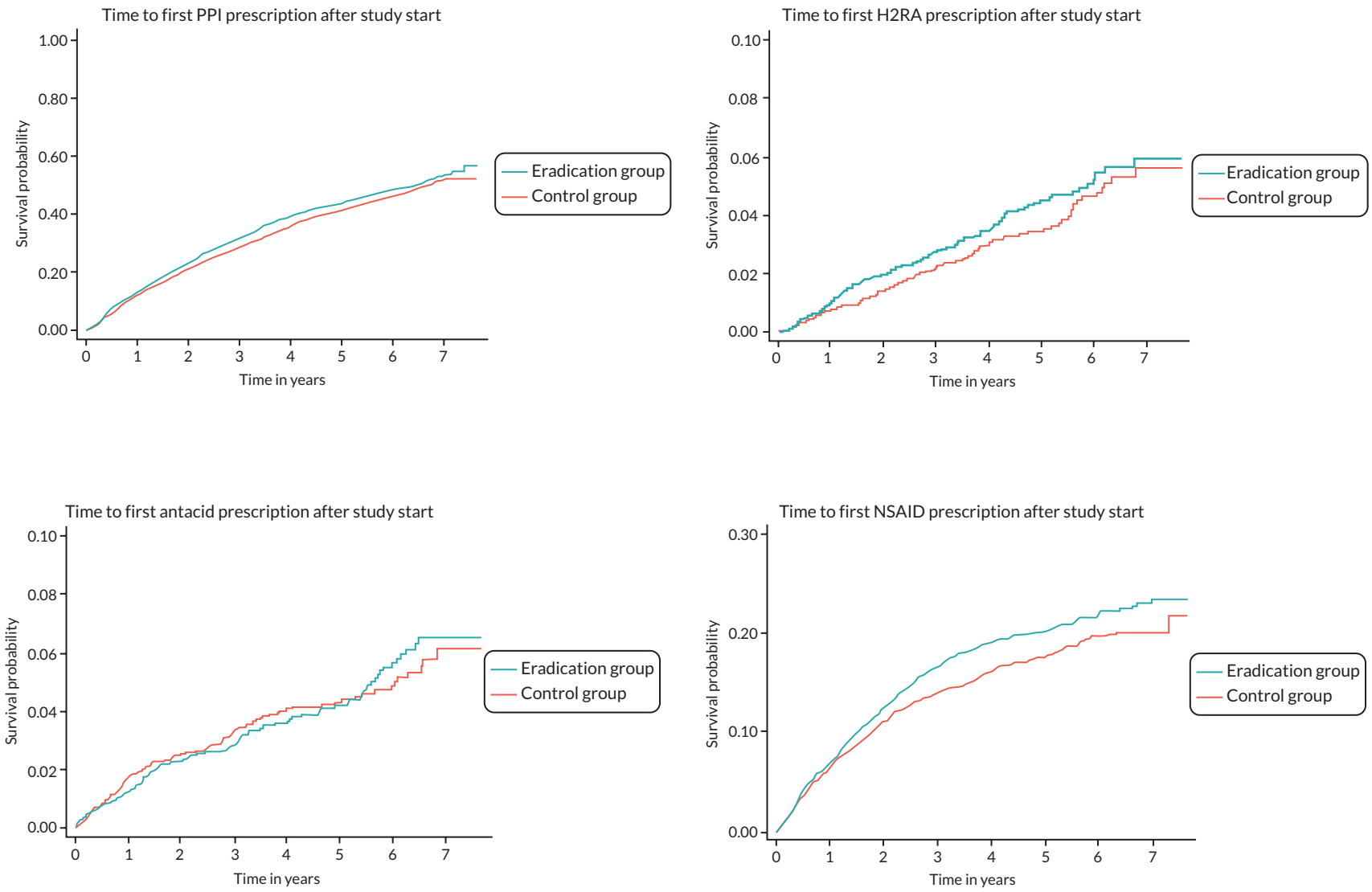


FIGURE 13 Kaplan–Meier curve of time to first prescriptions of drugs of interest.

TABLE 19 Hazard ratios for association of eradication from separate Cox models predicting time to first drug prescription during follow-up

Cox models predicting time to first prescription of drug	HR of effect of eradication vs. control	95% CI		*p*-value
PPIs	1.09	1.00	1.19	0.049
H2RAs	1.16	0.87	1.55	0.304
Antacids	1.02	0.78	1.33	0.909
NSAIDs	1.17	1.02	1.33	0.022
Stopping aspirin	0.98	0.91	1.07	0.705

TABLE 20 Cardiovascular outcomes

	HR	95% CI		*p*-value
Randomisation group				
Eradication vs. control	0.87	0.70	1.09	0.23
Study centre[a]				
Birmingham	1.10	0.79	1.53	0.57
Durham	0.87	0.62	1.22	0.41
Nottingham	1.00			
Oxford	0.80	0.54	1.18	0.27
Southampton	0.87	0.65	1.17	0.37

a Nottingham centre includes Belfast and Scotland.

Note
Test of proportional hazards assumption for randomisation group: $p = 0.200$.

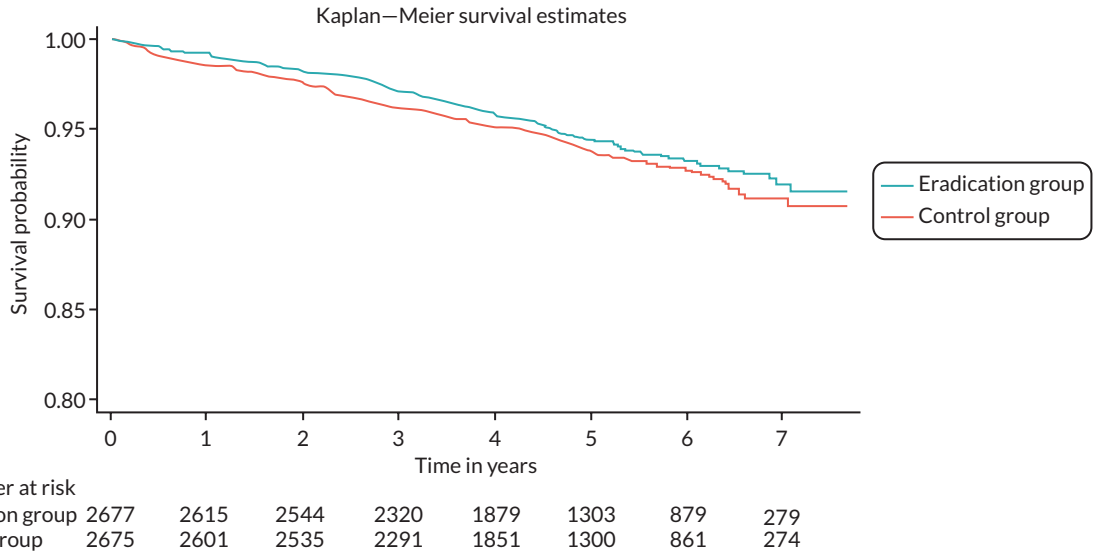


FIGURE 14 Kaplan–Meier survival curves: CV outcomes.

Serious adverse events

Three patients were hospitalised due to serious AEs (*Table 22*) thought possibly related to study medication [two in the active eradication group (extreme stomach pain and arrhythmia with hypertension) and one in the placebo group (oesophageal spasm)].

TABLE 21 Reported AEs

	Eradication group					Controls				
Category description[a]	All	Severe	Moderate	Mild	Unclassified	All	Severe	Moderate	Mild	Unclassified
(06) Unpleasant (metallic) taste in mouth/tongue discoloration	**766**	155	314	250	47	**19**	< 5	6	11	< 5
(17) Diarrhoea	**506**	81	213	199	13	**136**	17	49	70	< 5
(01) Nausea	**272**	48	100	111	13	**88**	6	30	51	< 5
(07) Furred tongue/dry mouth or throat	**202**	46	82	67	7	**31**	< 5	9	16	< 5
(04) Abdominal pain or discomfort	**283**	44	119	113	7	**130**	17	32	81	< 5
(13) Tiredness	**237**	41	117	68	11	**141**	19	57	58	7
(03) Flatulence	**178**	33	88	51	6	**61**	6	25	28	< 5
(10) Headache	**224**	27	98	92	7	**120**	11	39	67	< 5
(11) Dizziness	**176**	22	67	80	7	**65**	< 5	19	38	< 5
(09) Darkening of urine	**284**	21	125	113	25	**48**	< 5	15	30	< 5
(02) Dyspepsia	**117**	20	44	48	5	**89**	6	32	47	< 5
(15) Urticaria/skin rash/ itching	**69**	12	30	24	< 5	**55**	8	15	28	< 5
(05) Constipation	**64**	9	32	20	< 5	**69**	8	27	32	< 5
(08) Oral mucositis/thrush	**38**	9	21	8	< 5	**< 5**	< 5	< 5	< 5	< 5
(16) Flushing	**13**	< 5	< 5	8	< 5	**< 5**	< 5	< 5	< 5	< 5
(99) Other	**577**	122	243	162	50	**228**	33	77	99	19
Total	4006	692	1695	1414	205	1287	141	435	659	52

a Categories with at least five reports.

TABLE 22 Serious adverse events

Type of event	Causality	Treatment arm[a]
Hospitalisation – extreme stomach pains	SAR (possibly related)	Active
Hospitalisation – oesophageal spasm	SAR (possibly related)	Placebo
Hospitalisation – arrhythmia and high blood pressure	SAR (possibly related)	Active

SAR, serious adverse reaction.
a Not known at the time.

Deaths

In total, 657 participants died during follow-up (306 in the eradication group and 351 in the control group). Only 2 of the 657 deaths were recorded by ONS as due to peptic ulcer (one due to bleeding). The apparent difference in the number of deaths in each group prompted a post hoc analysis, which showed this did not reach statistical significance (HR 0.86, 95% CI 0.74 to 1.01; $p = 0.058$). *Figure 15* and *Table 23* show the ONS cause of death.

Malignancy was the most common cause of death and largely accounted for the numerical difference between the two treatment groups (see *Table 23*).

Deaths in participants with a primary end point

Fourteen patients (eight in the control group, six in the eradication group) who had a primary outcome event died during follow-up at a median of 480 (IQR 22–1166) days after their presentation with ulcer bleeding. Malignancy was the reported cause of death in six.

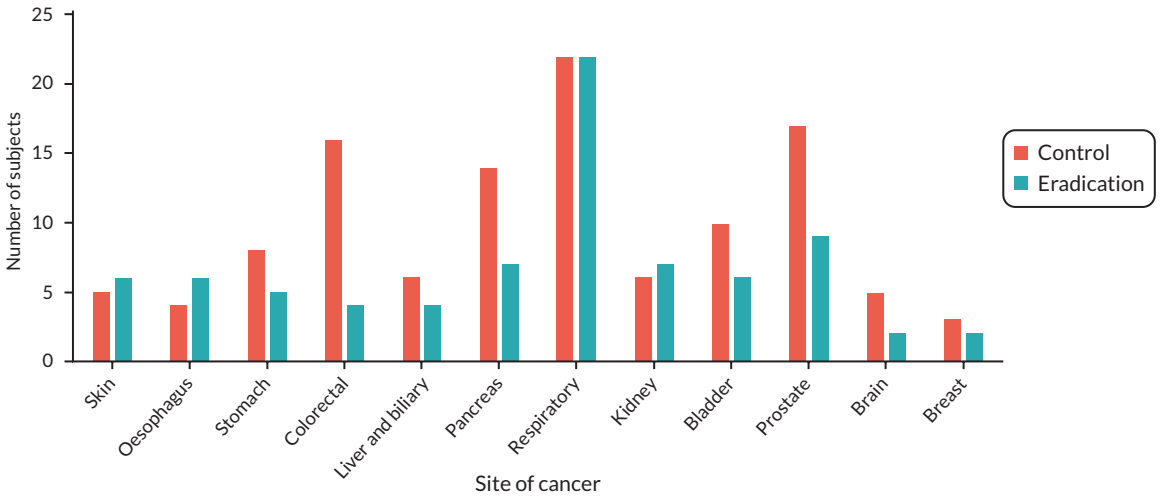


FIGURE 15 Cancer deaths by site.

TABLE 23 Office of National Statistics cause of death

System	Eradication	Control
CV	86	87
Respiratory	49	41
Central nervous system	15	26
Psychiatric	15	14
GI and liver	12	12
Malignancy	93	130
Haematological	12	14
Other causes	28	27
Total	306	351

Chapter 6 Health economics report

Introduction

When HEAT was being set up in 2011, peptic ulcer and its complications of bleeding and perforation were common. For many gastroenterologists, peptic ulcer disease had been the major entry in their casebook and a common cause of morbidity and mortality, resulting in total economic costs estimated at that time to be £15,000 per hospital admission.[75,76] Additionally, major clinical advances recognising the roles of *H. pylori* infection and NSAIDs in ulcer disease were being made too.

When HEAT was planned, there were concerns among gastroenterologists over the rising use of low-dose aspirin. Evidence was emerging for a pathogenic interaction with *H. pylori*, making eradication an attractive therapeutic target for which the HEAT study was established to investigate. To do so, recruitment numbers in any trial would need to be large because peptic ulcer bleeding is relatively uncommon. Meanwhile, industry-sponsored trials of cyclo-oxygenase 2 inhibitors had established that large numbers could be recruited in a community setting, but the costs of doing so were expensive, thus making it important to investigate whether the benefits produced were cost-effective.[5] Eradication of *H. pylori* in aspirin users was an attractive vehicle with which to test this paradigm. Aspirin use was high, and *H. pylori* still quite prevalent. Furthermore, the regimen of eradication treatment lasted a week, which reduced the challenges of drug supply and distribution when compared to a trial of ongoing treatment.

Unfortunately, several of the HEAT trial's key assumptions were not met, necessitating a study extension and recruitment of larger numbers of subjects. For example, the baseline prevalence of *H. pylori* (17.8%) was low compared to 22% in the pilot study, as too the primary outcome event rate during the trial was somewhat lower than expected and dyspepsia was very uncommon, suggesting mild disease. In addition to the reduction in statistical power which emanated from these factors, the biphasic nature of the response to treatment would further reduce the ability to take meaningful account of timing and durability of response. These issues made many of the trial's proposed analyses,[65] including economic analyses, unreliable because of low event rates and lack of statistical power.

In this analysis, we focus on key outcomes from the HEAT trial to measure net monetary benefit (NMB) due to the HEAT intervention. The main inputs into this calculation are monetised patient benefit, cost of a peptic ulcer bleed and prevention costs due to the intervention. We also explored the possibility of whether costs associated with all-cause secondary care may influence NMB.

Methods

Notwithstanding the plans given for economic analysis,[65] we tie our approach for analysis to the HEAT trial findings and outcomes on clinical effectiveness reported in earlier chapters. The first of these concerns the time horizon, up to 2.5 years beyond initial treatment, reflecting the significant reduction in incidence of the HEAT trial primary outcome in the active eradication group in follow-up, an advantage that becomes null with longer follow-up. The second concerns HEAT trial secondary outcomes – other clinically significant causes of GI bleeding, detected uncomplicated ulcers, GP-recorded dyspepsia, CV outcomes, target medications – where none of these in the active eradication group differed significantly from its counterpart in the control group at 2.5 years of follow-up. Third, consideration is given to the number of patients needed to be treated (NNT) to prevent one additional primary outcome peptic ulcer bleed at any time after the start of treatment, calculated using Altman and Andersen's[73] time to event method. In HEAT, the NNT was estimated to be high, NNT = 238, and its associated 95% CI wide.

Price inflation index

The price year is set to 2020–1, and the perspective of analysis is in the NHS and Personal Social Services. For inflating a prior year cost into 2020–1 prices, we used a forward inflator. This was calculated from annual inflation rates formed

by blending the NHS Cost Inflation Index (NHSCII) and the Hospital and Community Health Services Index (HCHS), both indexes supplied in section 15.3 in Jones and Burns[77] (*Table 24*).

Intervention

Implementation of the intervention across the population of patients – older people aged 65 + years regularly using low-dose aspirin – follows HEAT's screen and test-and-treat procedure:

- invitation to screen posted
- for acceptances primary care nurse administers the urea breath test
- postage of eradication treatment to those tested positive.

Active triple-therapy eradication treatment consisted of oral lansoprazole 30 mg, clarithromycin 500 mg and metronidazole 400 mg, all taken twice daily for 1 week by patients who screened positive to *H. pylori* using the INFAI *Helicobacter* test. The costing elements of the intervention were obtained from the April 2020 edition of the Electronic Drug Tariff and Jones and Burns,[77] and given in *Table 25*.

TABLE 24 Annual inflation (%) and 2020–1 forward price inflator

Financial year	NHSCII pay and prices[a]	2020–1 forward inflator[b]
2011–2	2.10	1.170
2012–3	1.70	1.151
2013–4	1.10	1.138
2014–5	0.90	1.128
2015–6	1.30	1.114
2016–7	2.12	1.090
2017–8	1.16	1.078
2018–9	2.31	1.054
2019–20	2.21	1.031
2020–1	3.08	1.000

a Tabulated for 2011–2 up to 2015–6 is the HCHS pay and prices inflation rate and for 2016–7 onwards NHSCII.
b Calculation: value 2019–20, 1 + 3.08/100; value 2018–9, (1 + 2.21/100)(1 + 3.08/100), etc.

TABLE 25 National Health Service cost elements of the intervention

Item	Cost £	Note
Urea breath test (INFAI)	21.70	INFAI test kit includes test analysis
Lansoprazole 30 mg	1.27	1 pack of 28 gastro-resistant tablets
Clarithromycin 500 mg	2.44	1 pack of 14 tablets
Metronidazole 400 mg	3.75	1 pack of 21 tablets
Primary care nurse	7.33	10 minutes (source: HEAT admin team) at £44 per hour
Screening invitation	2	includes provision for administration (source: HEAT admin team)
Postage of treatment	4	(source: HEAT admin team)
Total[a]	40.61	

a Drug costs apportioned to the 7-day course of the intervention total £5.58.

Prevention of peptic ulcer bleeds

To establish the cost to the NHS of the HEAT proactive screening programme for preventing peptic ulcer bleeds, we constructed a simple economic model that took the form of a decision tree, with its main outcome tethered to the NNT to avoid one hospitalisation due to peptic ulcer bleeding. In HEAT, estimated NNT = 238 (95% CI 184 to 1661). There were three main components: costs arising from invitations to take part in screening (£2, see *Table 25*); costs due to breath testing for those that came forward to be screened (£29.03, see *Table 25*); and eradication treatment costs (£9.58, see *Table 25*), including side-effect management (£39 for one GP consultation, Jones and Burns[77]), among those returning a test result positive for the presence of *H. pylori*. The baseline model is given in *Figure 16*. Screening letter postage and treatment postage were HEAT study parameters supplied by the HEAT admin team.

Transition probabilities were taken from the HEAT Consolidated Standards of Reporting Trials diagram and main analyses (see *Chapter 5*): response rate to screening invitation 16% (= 30,166/188,875), proportion returning a positive breath test 18% (= 5367/30,166). Proportion of treated patients experiencing side effects of any level of severity 70%, of which 10% consult their GP. Additional cost elements arising from active treatment concern the incidence and consequence of side effects and their management, the latter assumed done so by the patient's GP at £39 per consultation.[77]

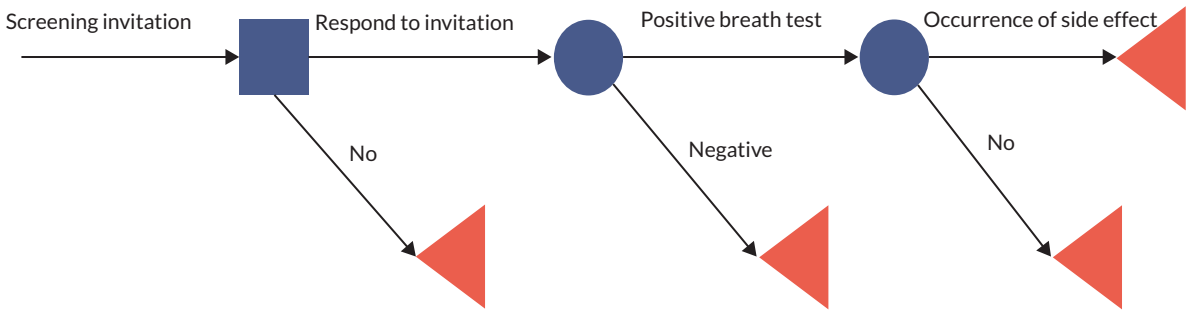
The scenarios that were considered illustrated improvements that would have reduced treatment cost when compared to baseline: screening invitations texted via phone rather than posted; every screening invitation taken up; the NNT set to the lower value of its estimated 95% CI; and doubling the positive breath test rate.

Comparator

The comparator is defined as there being no *H. pylori* screening programme, implying no treated patients generating no prevention whatsoever. In terms of cost, the comparator has no implementation costs.

Peptic ulcer bleeding

The primary outcome of HEAT was the incidence of definite or probable peptic ulcer bleeding, as determined by the masked HEAT adjudication committee using primarily HES data. For a patient to be deemed as having been hospitalised, there had to be a relevant HES record. Those that were inpatients for other reasons who were transferred to the gastroenterology service were also included. Our HES data on bleeds was for admitted patient care only; it did not include fields recording ambulance conveyance or emergency room use that may have occurred immediately prior to that admittance.



Decision tree model parameters	Base case (estimated from trial)	Alternative scenario values
NNT to avoid peptic ulcer bleed hospitalisation (patients)	238	184
Invitation cost	£2.00	£0
Response to invitation %	16%	100%
Breath test cost	£29.03	Not altered
Positive breath test %	18%	36%
Eradication costs	£9.58	Not altered
Eradication side effects %	7%	Not altered
Eradication side-effect cost	£39	Not altered

FIGURE 16 Decision tree model.

The cost of peptic ulcer bleeding was determined as the mean reimbursement of the hospital stay in which it occurred, plus any related follow-up stay. If the adjudicated date of the GI bleed occurred partway through the stay, cost was apportioned from that date.

Follow-up secondary care costs arising from a peptic ulcer bleed were determined using patient HES data. Consultation with the HEAT principal investigator identified follow-up management events associated with all initial bleed events. Our HES data on bleeds were for admitted patient care only; they did not include fields recording ambulance conveyance or emergency room use that may have occurred immediately prior to that admittance.

Exploring sources of cost

We assessed the substantive components of the costs, to identify if there were any key areas to examine in more detail. We analysed secondary care inpatient admissions of HEAT participants observed post randomisation as recorded in HES data. Costings by hospital stay were assigned as the average reimbursement according to Health Resource Group (HRG) code as identified in NHS Reference Costs schedules. In addition to all-cause admissions, we also analysed costs of admitted stays coded to the gastroenterology specialty. Comparison was by randomised treatment groups, as well as a second comparison designed to account for adherence to active trial treatment.

Utility

At baseline, a random pre-selected 10% of HEAT participants were invited to complete EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS), with follow-up at the end of the trial. Health-related utility scores were assigned using the National Institute for Health and Care Excellence (NICE)-recommended 5L-3L crosswalk algorithm.[78] The dates on which the two questionnaires were filled out varied, some filled out prior to the start of treatment, some filled out during treatment and into the interval 4 weeks after that, and some filled out more than 4 weeks beyond the completion of treatment. Those filled-out surveys prior to treatment were used to compare with those recorded post treatment to test for utility decrement due to side effects arising from active treatment. A second analysis, profile analysis,[79] was used on HEAT participants providing responses at baseline and at end of trial follow-up. A third analysis formed the utility data as a two-wave unbalanced panel – participant by survey questionnaire. We were able to exploit the data feature that the time-gap separating questionnaire responses was irregular and varied substantially across individuals, enabling specification and estimation of the following simple fixed-effects model:

$$utility_{ij} = \beta_0 + \beta_1 age_{ij} + \alpha_i + u_{ij}$$

where *i* indexes individual and *j* survey, αi is a fixed individual effect, *uij* is an idiosyncratic error and data *ageij* is the age in years when respondent *i* completes survey *j*. The model was fitted with the time-demeaning fixed-effects estimator with robust standard errors (Stata version 18). The model was used to predict mean utility given respondent age across our population of interest.

Finally, patient benefit due to avoidance of hospitalisation for a peptic ulcer bleed forms part of the calculation of NMB. Using area under the curve, representative monetised patient benefit can be calculated on an individual basis and aggregated across participants as the product of the NICE quality-adjusted life-year (QALY) threshold (lower limit £20,000) by the area:

$$AUC = \frac{14(U_0 - U_2)^2}{365\,(U_1 - U_2)}$$

Where *U0* is the disease-free utility level predicted for a given age using the fixed-effects model, *U1* is a literature-sourced utility level (set 0.735 at 28 days post bleed[80]) and *U2* is the initial disease-onset utility level. Note that $U0 > U1 > U2 \geq 0$, a fixed constant recovery rate is assumed, and the area is that of a triangle with vertices in (utility, time in days) space as follows: (*U0*,0), (*U2*,0), (*U0*,T), where (*U1*,28) lies on the hypotenuse; scaling by 365 gives the annualised per-patient benefit.

Data

NHS Digital supplied episodes of all-cause admitted patient care extracted from HES linked to the HEAT patient cohort. The admission types were: day case, regular, elective inpatient, non-elective inpatient. The NHS service providers included acute hospital trusts, mental health trusts and private hospitals (when treating NHS patients). The extract of episodes corresponded to admissions that had discharge dates occurring within the period beginning April 2011 up until the end of June 2020.

Among the variables included in the extract were:

- admission type, this being either emergency and non-elective or elective. If an elective admission, further breakdown into ordinary elective, day-case and regular admission, relied on the episode codes supplied for patient classification and intended management.
- 20 ICD-10 (5th edition) diagnosis code variables (i.e. first in sequence is the primary code with up to 19 additional codings used as required).
- 24 Office of Population Censuses and Surveys 4 (April 2021) classification of interventions and procedures (i.e. first in sequence is the primary code with up to 23 additional codings used as required).

For purposes of costing, data were organised by hospital stay; where all episodes of care pertaining to a given stay were bundled together into the sequence in which they were recorded.

Cost of stay

The HES extract was organised by stay and batched by financial year according to discharge date. For a given financial year, the cost of each stay was estimated as the mean NHS reimbursement according to the following procedure:

1. Use the NHS HRG4/4 + Costing Grouper programme to derive lookup HRG codes for stays.
2. For each stay, the lookup HRG code was then matched to NHS Reference Costs and the mean NHS reimbursement due to that code, taken from the appropriate schedule, was imputed as the cost of the stay.

Healthcare Resource Group 4/4 + Grouper

The HRG4/4 + Costing Grouper programmes and documentation are released annually by NHS Digital, with the current version (2022–3) linked at NHS Digital Groupers. The older versions that we use, starting with the 2011–2 HRG4 programme and proceeding up to the 2020–1 HRG4 + version used for those admitted care stays with discharge dates during April–June 2020, are available as recent and older archived content linked at NHS Digital Grouper archive. Output from the Grouper was used to:

- assign a HRG code to each stay
- identify any unbundled cost items associated with a stay
- assign a short/long-stay flag depending on the length of stay in relation to its trimpoint, or assign Finished Consultant Episodes (FCE) trimpoint if a stay was represented by a single episode.

Not all the variables needed to run the Grouper were included in our HES extract. For example, discharge method and patient destination upon discharge, respectively, the variables labelled 'DISMETH' and 'DISDEST', were omitted. To enable computation, we created DISMETH and, in every case, imputed its value as 1 (1 = patient discharged on clinical advice or with clinical consent), which is taken from its set of permissible values; similarly imputed was DISDEST = 19 (19 = usual place of residence). Also, counts of days of rehabilitation, specialist palliative care or critical care were missing from the HES extract and accordingly were set to 0, but replaced by per diem unbundled HRG multipliers when those were recorded.

National Health Service reference costs

National Health Service Reference Costs schedules and documentation are released by NHS Digital, with the latest schedules available at NHS National Cost Collection along with links to earlier collections. After grouping, the stay is

costed according to the mean reimbursement tabulated for the assigned HRG code, appearing in the schedule indicated by its admission type. Per-day excess bed costs were added for stays prior to 2018–9 in instances when the length of stay exceeded the spell trimpoint applicable to that code. From 2018 to 2019 onwards, FCE mean reimbursements were used irrespective of the number of episodes constituting the stay; as well, trimpoint adjustments were no longer applied.

Cost was imputed for some HRG codes lacking national prices. Most notably for LA97A 'Same Day Dialysis Admission or Attendance, 19 years and over' as well as COVID-19 infection DX(0–2)1A observed in financial year 2020–1 of our HES extract. For the former, cost was imputed as the session weighted average of LD0(1–8)A listed in renal schedules. For the latter, cost was approximated using the Secondary Uses Service HRG code supplied with the HES extract with lookup to the 2019–20 non-elective long-stay schedule followed by forward inflating to 2020–1 prices.

Total cost

Total cost per HEAT participant was defined as the sum of costs of admitted hospital stays that occurred during 2.5 years of follow-up, and analysed using descriptive statistics. Means are recorded alongside of which the approximate normal-based 95% CI is given. Medians are recorded alongside of which the IQR, reported as the 25th–75th percentile, is given. When compared by group, testing for difference in means was by two-sample *t*-test, and testing for difference in distribution was by Wilcoxon rank-sum test. Distributions are plotted in two forms: frequency histogram and smooth normal kernel density plot. Semilog regressions are used to model the natural logarithm of total cost depending on individual participant factors, including sex, age at bleed, years since randomisation, length of hospital stay due to bleed, as well as assigned treatment group.

The comparisons we considered were:

- As per allocation at randomisation: 'eradication' being the group of people who received active treatment to eradicate *H. pylori* versus 'control' being those people receiving placebo – that is, groupings as per ITT.
- Denoted 'eradication*' and being the subgroup of those in eradication who adhered to active treatment versus 'control*', where the latter adds to control those participants that were nonadherent to active treatment.
- Eradication and control when applied to admissions designated to be under the gastroenterology specialty.
- Eradication and control when applied to admissions in which a GI bleed, pertaining to the HEAT study primary outcome, first occurs and is managed.

Results

Prevention of peptic ulcer bleeds

At baseline settings, to provide active treatment to exactly NNT = 238 people requires screening invitations be made to 8376 people (= 238/(0.18 × 0.16)), of whom 1338 (= 8376 × 0.16) are expected to respond for breath testing. At baseline prices, providing 8376 invitations costs the NHS £16,751, breath testing costs £38,838 and providing active treatment costs £2280, summing to £57,870. Adding in further costs due to the side effects from eradication £650 (= 238 × 0.7 × 0.1 × £39) finds, at baseline, the NHS incurring approximately £58,500 to prevent one GI bleed costing on average £3790.

For a scenario in which screening invitations are free-texted rather than posted, screening costs halve, but overall prevention cost still exceeds £50,000. A second scenario, imposing that all screening invitations are accepted, heavily reduces screening costs, but overall prevention costs are still substantial, exceeding £44,400. A third scenario, imposing NNT= 184 (the lower value of its estimated 95% CI) overall prevention cost, reduces to just above £45,200. A fourth scenario, doubling the rate of positive breath tests to 36%, brings prevention cost down to £30,700. Common to all scenarios is that despite each improvement, the costs to prevent one GI bleed still substantially outweigh the cost of occurrence.

Peptic ulcer bleeding

Forty-four participants, 18 in eradication and 26 in control, experienced the trial primary outcome. There were 33 cases, in which admission resulted in at least 1 overnight stay in hospital (including 4 cases where the bleed occurred in hospital), 9 coded as day-case and 2 as short-stay admissions with length of stay as 0 days. The distribution of length of stay of individual participants due to peptic ulcer bleeding is shown in *Figure 17*. The median length of stay was 2.5 days

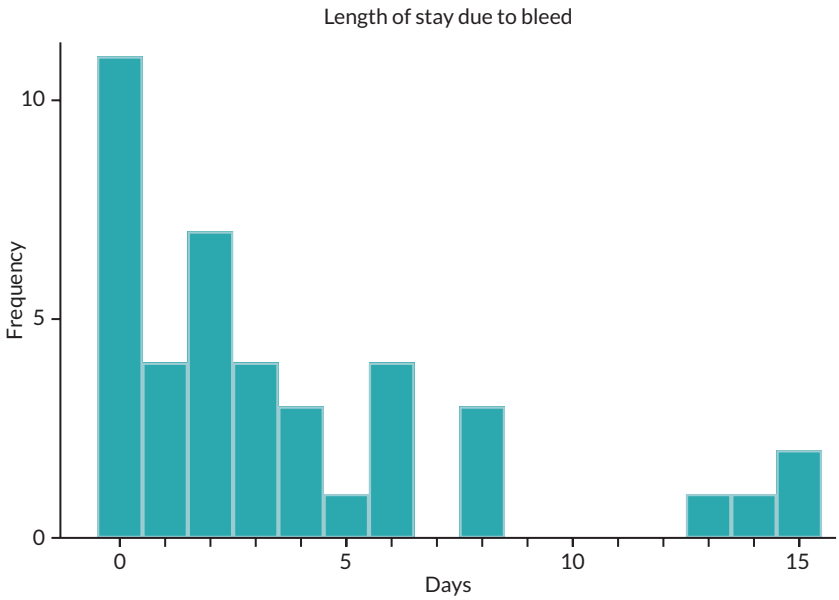


FIGURE 17 Length of hospital stay due to GI bleed.

(IQR 0.25–6 days), and across the 33 cases in which admission resulted in at least one overnight in hospital, the median length of stay was 4 days (IQR 2–8 days).

The cost of an ulcer bleed was equivalent to the cost of the index hospital stay in 23 cases. In 16 cases, it was the index stay plus the cost of follow-up care (all follow-ups were day-case admissions for endoscopy examination), of which 3 cases involved multiple follow-ups. There were four cases in which the ulcer bleed occurred partway through the hospital stay for which cost was apportioned. Finally, in one case, cost was imputed as the index hospital stay was outside the UK.

The mean of observed per-patient total cost in 2020–1 prices was £3516 (95% CI £2526 to £4505), and the median £2865 (IQR £1045–£4438). By group, there was no significant difference in total cost either in mean $p = 0.657$ (eradication mean: £3790, 95% CI £2117 to £5462; control mean: £3326, 95% CI £2094 to £4559) or by distribution $p = 0.662$ (eradication median: £2605, IQR £1315–£5718; control median: £2,897, IQR £1039–£4232).

Estimation results for two semilog regression models are reported in *Table 26*. Whether individuals were separated into eradication/control or into adherence modified eradication*/control* groups, the length of stay was the only significant driver of cost.

All-cause cost

From our HES extract, with discharge dates framed to April 2011–June 2021, a total of 20,621 stays of all-cause admitted patient care were recorded on HEAT participants. Of these, 4732 occurred either prior to the date of study randomisation or after the date of any withdrawal from the study and were therefore removed from further consideration. This left 15,889 stays, of which 7657 were recorded by participants randomised to the eradication group and 8232 by participants randomised to control.

Viewing stays by participant (totals of 2677 in eradication and 2675 in control): in the eradication group 1781 participants recorded in total 7657 stays of admitted care, and thus the remaining 896 participants in this group had no recorded stay. In control, 1752 participants recorded stays and 923 none.

All-cause cost – follow-up over 2.5 years

There were 1219 eradication participants who recorded one or more all-cause admitted care stays in the period up to 2.5 years beyond their respective dates of randomisation. The remaining 1458 in eradication comprised: 896, that by the end of the study had yet to record any stay whatsoever, and 562, for whom every discharge date occurred

TABLE 26 Semilog least squares regression of total cost of bleed

Parameter	Model 1 Estimate (std err)	Model 2 Estimate (std err)
Eradication (= 1, control = 0)	−0.116 (0.254)	
Eradication* (= 1, control* = 0)		−0.283 (0.291)
Length of stay (days)	0.038[a] (0.012)	0.039[a] (0.012)
Sex (F = 0, M = 1)	−0.151 (0.329)	−0.119 (0.318)
Age at bleed (years)	0.003 (0.016)	0.007 (0.016)
Time since randomisation (years)	0.050 (0.068)	0.054 (0.065)
Constant dummy	7.475[a] (1.416)	7.093[a] (1.433)
Sample size	44	44
R-squared	0.366	0.379

F, female; M, male.
a Significant $p < 0.05$.

more than 2.5 years after randomisation. The corresponding number in control over 2.5 years of follow-up was 1218 participants.

Averaging the per-participant total cost of all-cause admitted care across 2.5 years of follow-up for the $n = 1219/1218$ eradication/control participants with at least one stay recorded yielded, respectively, £5736 (95% CI £5294 to £6178) and £5601 (95% CI £5035 to £6167); these means were not significantly different ($p = 0.713$). The sample medians, respectively, £2581 (IQR £1017–£7559) and £2460 (IQR £1011–£6599), are considerably less than their corresponding means, indicating that the distribution of total cost is skewed; however, the two distributions did not differ significantly ($p = 0.514$); this can be verified by inspection of the kernel smooth distributions of total cost by participant and group given in *Figure 18*.

Adherent to eradication

Eradication* participant numbers totalled 956 and control* 1481. Total costs of the redefined groups now averaged: eradication* £5456 (95% CI £4965 to £5947) and control* £5806 (95% CI £5307 to £6305), and again the difference in means was not significant ($p = 0.352$). Any differences in the distributions of total cost were not significant ($p = 0.241$) with median eradication* total cost £2463 (IQR £984–£7181) and control* £2648 (IQR £1039–£7058).

Gastroenterology specialty

Eradication participants admitted and/or treated under gastroenterology specialty care numbered 149 when follow-up was over 2.5 years, with mean/median total costs, respectively, £3563 (95% CI £2609 to £4516) and £1058 (IQR £580–£2968). In control, 122 participants with mean/median £3641 (95% CI £2253 to £5030) and £974 (IQR £583–£3148). Testing indicated that the difference in mean remained not significant ($p = 0.925$) as too in distribution ($p = 0.945$).

Utility

Overall, 742 complete responses to EQ-5D-5L and EQ-VAS were received, of which 2 (being the initial and end-of-study follow-up questionnaires) were received from each of 268 HEAT participants. Responses received only to the initial request numbered 174, while 32 responded to the follow-up request but not the initial one. There were five responses received from four HEAT participants with a trial primary end point, but none of these were dated either at or near the time of the event.

Organised by eradication/control responses numbered 367/375. Further broken down into initial and follow-up, in *Table 27*, listed are group means and 95% CI for crosswalk utility score and health today EQ-VAS score.

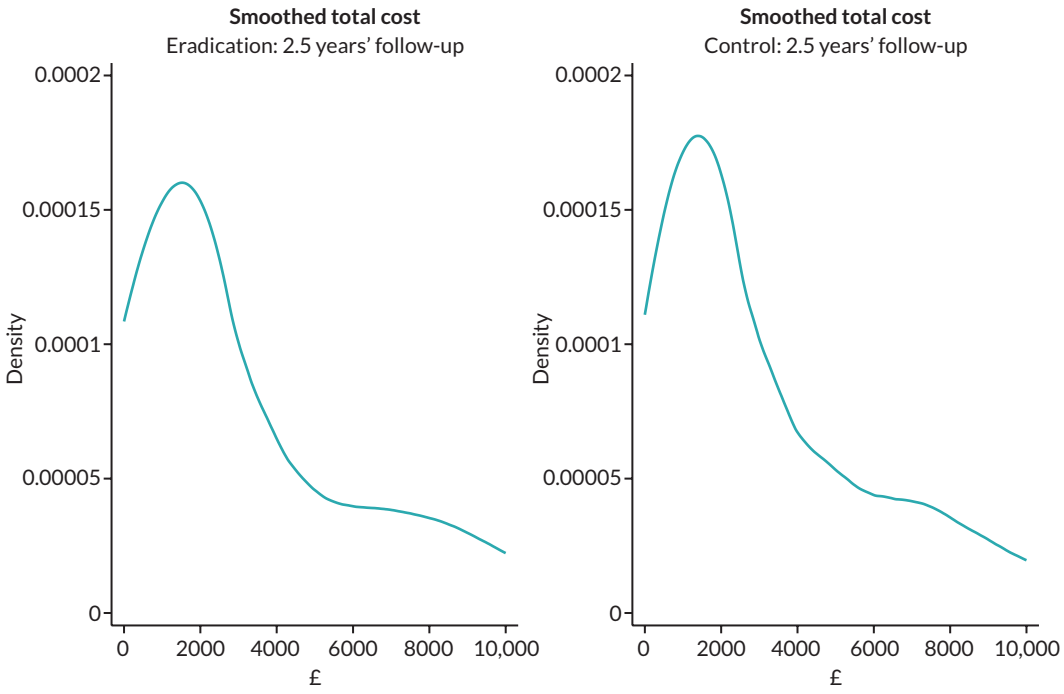


FIGURE 18 Kernel smooth distribution of total spell cost.

TABLE 27 Mean crosswalk utility score and VAS health today score by eradication/control and period (95% CI in parentheses)

	Eradication		Control	
	Initial	Follow-up	Initial	Follow-up
Utility score	0.809 (0.782 to 0.836)	0.777 (0.742 to 0.812)	0.824 (0.799 to 0.849)	0.811 (0.783 to 0.840)
Health today	81.0 (78.9 to 83.2)	78.7 (76.0 to 81.5)	82.4 (80.3 to 84.5)	81.5 (78.7 to 84.3)
Total	222	145	220	155

Focusing first on initial responses, a total of 442 were received. Of these, 380 had completed their EuroQoL questionnaire within 4 weeks of starting treatment; 50 completed prior to starting treatment; and the remainder, 12, had completion dates more than 4 weeks beyond having commenced treatment. Among those responding within the 4-week treatment window, 129 in eradication had also reported an adverse treatment-related event: group mean utility score 0.792 (95% CI 0.756 to 0.830). The two-sided *t*-test comparing this affected group to the 50 who had yet to start treatment when they completed the questionnaire and were therefore treatment-unaffected – group mean utility score 0.822 (95% CI 0.767 to 0.878) – found the difference in means not significant, $p = 0.398$.

Next, for those providing initial and follow-up pairs of EQ-5D responses, results of Pareto classification of health change by eradication/control are given in *Table 28*. The most frequent health change state is 'worsen' – 54 in eradication and 55 in control – this, however, is to be expected, as, for most respondents, there was a substantial time gap between EQ-5D completion dates, averaging almost 4 years. Comparing observed health change distributions, there was no significant difference between eradication and control, $p = 0.749$.

Absent of a statistically significant difference in utility between eradication and control, a fixed-effects model was fitted across the combined sample resulting in (standard errors in parentheses):

TABLE 28 EuroQol-5 Dimensions profile analysis by eradication/control

Health state change	Eradication	Control
Improved	23 (17.4%)	20 (14.7%)
No change	41 (31.1%)	41 (30.1%)
Worsen	54 (40.9%)	55 (40.4%)
Mixed	14 (10.6%)	20 (14.7%)
Total	132	136

$$\widehat{utility} = \underset{(0.185)}{1.861} - \underset{(0.002)}{0.014}age$$

(N = 474, NT = 742, R^2 = 0.015). Here the utility decline with age is statistically significant (t = −5.7, p < 0.01).

Using the average prediction at, for example, age 70 (being U_0= 0.881), the monetised patient benefit at the lower bound of the NICE threshold (£20,000/QALY) is maximised at £810. Added to the cost saved by avoiding one GI bleed (being £3790) yields a patient benefit that is outweighed many times over by the costs of preventing that one bleed. The NMB of the intervention is, therefore, negative-valued and the intervention judged to not be cost-effective, as the costs to avoid one GI bleed far outweigh the monetised benefits of preventing that bleed.

Chapter 7 Discussion

Our study had three main aims: medical (discussed here), health economic (discussed in *Chapter 7*) and methodological (discussed here). The medical aim was to test the hypothesis that a 1-week course of *H. pylori* eradication in patients using aspirin ≤ 325 mg daily would reduce the incidence of subsequent adjudicated peptic ulcer bleeding that results in hospitalisation or death.

Summary of clinical results

In this study, we achieved high rates of *H. pylori* eradication when evaluated by follow-up breath testing, but there was also a higher-than-expected rate in the control group. We showed evidence of benefit with a 65% reduction in hospitalisation due to peptic ulcer bleeding over 2.5 years in patients in the eradication group compared with the control group. This was attributable to reductions in gastric and duodenal but not oesophageal ulcer bleeding. However, the protection against ulcer bleeding appeared to be lost with longer follow-up periods. There was no significant difference in the incidence of uncomplicated ulcers or thrombotic CV events, and the incidence of consultations for dyspepsia was low. A large number of AEs was reported by those in the eradication group while receiving treatment probably reflecting the active collection of data. As expected, a substantial number of patients died during follow-up, but competing risks analysis showed our results for eradication treatment remained significant if adjusted for ongoing death rates. There was a trend towards fewer deaths in the eradication group.

Significance in the context of previous studies

Prior to HEAT, there were clear observational data strongly associating *H. pylori* with aspirin-associated peptic ulcer disease and ulcer bleeding,[55–58] but very few data, establishing a causal link to support a policy of eradication. The main direct controlled evidence of causality came from one pivotal clinical trial reported by Chan and colleagues in patients who were enrolled because they had an index clinical bleed.[60] This found a 6-month incidence of ulcer rebleeding following *H. pylori* eradication (1.9%) that was not significantly different from that with omeprazole coprescription. (0.9%). For NSAIDs, there was a higher rebleeding rate (18.8%) and a significant reduction (to 4.4%). The lack of a placebo group in this study means the authors' conclusions are open to challenge. An alternative explanation is that omeprazole was superior to eradication in both aspirin and NSAID users, but missed significance with aspirin because event rates were lower. A similar comment can be made about the data from the subsequent long-term cohort study, where differential demography between the three cohorts further compromises the case.[62] Moreover, the rate observed in the cohort study in the average-risk patients (6.6 per 1000 person-years) was higher than seen in our control group (2.7 per 1000 patient-years) in the first 2.5 years, and the rates seen with eradication (9.7 per 1000 person-years) were higher than seen with HEAT (0.92 per 1000 person-years). These differences are attributable to the higher risks in a population that has already presented with ulcer bleeding, but the higher rate in those that have not may indicate national differences in the pathology of *H. pylori* infection. Moreover, in the trial from Lai and colleagues,[61] there was indeed a higher rebleeding rate (over 1 year) with eradication alone (14.8%), compared to use of lansoprazole (1.6%). HEAT extends evidence into the much broader population whose trial entry was not driven by a protocol requiring recent ulcer bleeding for trial entry. Our results show a significant protection over 2.5 years which appeared to be virtually total over 18 months, putting our data in accordance with the general conclusions of the Chan trial. With longer follow-up breakthrough, bleeding occurred resulting in a result which, although to a protocol not directly comparable, was more in line with the results over 1 year from Lai and colleagues. Epidemiological evidence suggests that risks of ulcer bleeding are high during the first year of aspirin use.[13–15] An investigation of *H. pylori* eradication in aspirin-naive people starting the drug for the first time would be an appropriate scenario for future research.

Effect of concurrent drugs

HEAT was a real-world study, and changes in the background use of drugs had the potential to confound and invalidate our conclusions. Changes in prescribing, including withdrawal of aspirin, or commencement of gastroprotective or ulcerogenic drugs, were allowed as clinically indicated or recommended by consensus guidelines. During the time that HEAT was being conducted, these became more conservative, as studies failed to demonstrate net benefit in some groups, particularly in patients without evidence of established CVD. This resulted in 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.[10] Also, during this time, use of antisecretory drugs for protection against aspirin-associated ulcer disease grew as the results of trials became incorporated into guidelines. These trends had an impact on HEAT as aspirin use fell, and PPI prescription rose with increasing duration of follow-up and had the potential to invalidate our results. However, differences between the two treatment groups remained significant in analyses allowing for such drug use.

Control group eradication

Ninety-one per cent of participants in the eradication group had a negative breath test at follow-up, suggesting that the treatment regimen we used was highly effective. However, short treatment regimens based on clarithromycin are not currently recommended because of the prevalence of clarithromycin resistance.[3] This makes the effectiveness of treatment in the study surprising. One theoretical possibility is that aspirin, via its effect on mucus and the gastric mucosal barrier, facilitates antibiotic delivery to the sites colonised by the organism.[81]

Twenty-four per cent of those in the control group also had a negative breath test at the end of the study. This is higher than has been seen in other community-based studies from the UK and Asia,[82–86] where reported levels of eradication in placebo control groups have ranged from 5% to 16%. However, these studies have assessed eradication after 6–24 months, compared to our study where the median interval was nearly 4 years. We found no evidence of out-of-study eradication treatment in our control group, but there was a higher incidence of incidental antibiotic exposure, specifically clarithromycin in control group participants with a negative end-of-study breath test compared to those where it remained positive.

Loss of benefit

H. pylori eradication appeared to offer complete protection in the first 17.5 months. Beyond that time, there started to be a breakthrough of ulcer bleeding in the eradication group. It is possible that reinfection or recrudescence could have occurred, but this is uncommon beyond adolescence, and the time course makes these possibilities unlikely. The same is true with regard to a prolonged effect of lansoprazole from the eradication regime. It is unclear why loss of protection occurs. *H. pylori* provokes an inflammatory response in the mucosa with an associated production of prostaglandins and other inflammatory mediators.[87] Prostaglandins are protective to the mucosa, and it is conceivable that loss of this mechanism could occur and lead to a paradoxical net reset of ulcer risk. We have identified one epidemiological study that found the risk of rebleeding in aspirin users was significantly higher in *H. pylori* negative, compared to positive individuals. Like us, the authors speculate that differences in endogenous prostaglandin synthesis may play a role.[88] However, there are no data as to whether this can occur in a context of aspirin use. Another theoretical possibility relates to acid secretion, which can, under some circumstances, increase following eradication.[89]

Secondary outcomes

Ulcer site

We subjected our primary outcome data to an analysis restricted only to gastric and duodenal ulcer bleeds, because there is evidence that oesophageal ulcer disease has a different pathogenesis. This analysis was strengthened by exclusion of ulcer bleeds from the oesophagus consistent with evidence that *H. pylori* does not promote and may even protect against oesophageal pathology.[90]

Uncomplicated ulcers

There were no differences between the treatment groups in the other secondary end points, 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.

The incidence of dyspepsia was very low, compared to that reported in comparable studies.[82,84,91–93] There may be a number of reasons for this. Importantly, use of antisecretory drugs at baseline was a contraindication to trial entry. The

effect of *H. pylori* eradication on dyspepsia has been controversial. There appears to be a small benefit,[91,93] but we did not find a difference between our treatment groups.

Thrombotic cardiovascular events

We recorded 318 events with ICD-10 codes for thrombotic CV events, principally MI, TIAs and strokes, suggesting an absolute risk of 0.12% pa, an order of magnitude lower than reported by meta-analyses of clinical trials.[9,24] However, it is likely that our strategy of using unadjudicated ICD-10 data led to some underdetection. It seems our population had a relatively low rate and did not differ between the treatment groups.

Safety

HEAT's primary outcome represents an evaluation of the GI safety of aspirin. The AEs collected refer to the safety of the eradiation treatment regimen, not the aspirin that all participants received. In order to avoid confusion and in accord with HEAT's MHRA classification as a Type A trial, AEs were only collected over 4 weeks from the start of dosing. The medium for reporting was the treatment diary recording the timing of drug use. This proactive approach resulted in a large number of reports of previously recognised individual symptoms and a threefold difference between the two treatment groups.

Deaths

Two issues stand out. Peptic ulcer bleeding was not the leading cause of death. There were only two cases in the entire population where peptic ulcer was the recorded as the cause of death and only one attributed to ulcer bleeding. Those developing the primary outcome of ulcer bleeding were more likely to die and at an earlier time point than was overall the case, but, with one exception, this was for causes other than ulcer disease (six due to malignancy). This pattern is in accord with data from Hong Kong, where there was only one death attributable to GI bleeding (in the average-risk group) over 5048 person-years.

The second issue of note was an apparent difference in the number of deaths between the treatment groups. This did not reach statistical difference and could have occurred by chance in a trial of this size, and our treatment groups were well balanced at baseline. Numerically, the difference is attributable to differences in the number of deaths registered as due to malignancy. *H. pylori* is clearly recognised as the dominant cause of gastric cancer worldwide.[94,95] The same cannot be said for other cancers. A recent meta-analysis has suggested that *H. pylori is* associated with an increased risk of colorectal cancer.[96] However, in the absence of the kind of meaningful narrative about possible pathogenic mechanisms that exists for gastric cancer, the association may not be causal.

Interestingly, the Hong Kong cohort study reports a significant excess of deaths not due to CV or GI bleeding causes in the *H. pylori* eradicated group that is principally attributable to cancer (6.4% vs. 1.7% in the *H. pylori* negative and 3.4% in the average-risk cohorts).[62] Therefore, it is possible that there is, in people who take aspirin, a previously unrecognised influence of *H. pylori* that warrants further investigation.

Methodology

Our aim was to establish a methodology for enrolment to large simple outcomes studies using electronically extracted primary care and follow-up using routinely collected primary and secondary care data, to reduce costs to a level that enables outcomes studies of clinically important questions to be done without the need for industry support.

This challenging goal was partially met, but lessons were learned along the way. The digital protocol for practice enrolment, the identification of suitable patients, the mechanics of upload of information and integration of primary and secondary care data worked well. A large network of generally positive general practices was developed. The numbers of patients contacted and enrolled were close to those that the trial set out to achieve, but this was over a longer-than-planned period of time suggesting that we were overambitious. Proportionately, greater or more effective deployment of resources may be needed for future studies.

Nevertheless, the cost of mounting HEAT was less than the cost of industry studies of comparable size. One widely quoted report suggests a price tag of $2.6 billion for all components of new prescription drug development and launch.[97] A more conservative estimate from the Institute of Safe Medicine Practices (ISMP) estimates a median cost

per trial of $19 million with trial size being one of two main influences.[98] The median cost per patient was estimated at $41,413, which is approximately two orders of magnitude higher than that for HEAT.

The other main cost driver in the ISMP study was the number of follow-up visits made. This represents an area for major cost saving from use of routine clinical data but is bought at the cost of the relative imprecision in GP records alone. The limitations of such an approach are illustrated by the fact that a primary outcome was only detected from the primary care record in 14 (31.8%) of cases. While HES data fill this information gap, this came at the cost of speed of acquisition.

In HEAT, HES data were supplied on an annual basis, but a need for detailed central verification before release meant that outcomes data were typically not available for adjudication until a year or more after they had occurred. This made it impossible to get anything like real-time supplementary information for adjudication or event-related information from patients. This should improve as NHS Digital moves towards monthly updates, which should be formalised in future studies. Also to be welcomed is the release of provisional data which are later ratified. A generic protocol which captures this process in the context of a clinical trial should be developed.

There were also delays in the acquisition of primary care data. This occurred because the GP had to upload data episodically and the extent to which this happened and was affected by other demands on the practice. The requirement for final data uploads coincided with the COVID pandemic and was only achieved in 714 (68.5%) of practices. In 14 cases, final data upload was not possible because the practice had closed. In this respect, development by TCR of an automated SNOMED-based system now supplies data on a virtually continuous real-time basis, which has cut out the need for practices to do follow-up data uploads.

Involving general practitioners, their staff and the public

Clearly, a trial methodology based in primary care needs to be attractive to GPs and their staff. It was not particularly difficult to assemble a large network of participating practices. Many signed up to further participation in similar research projects. In an evaluation of 149 HEAT trialists in the East Midlands, 119 (79.8%) participated in between one and three more similar trials (unpublished data). We also conducted a questionnaire study alongside our initial pilot of potential participants to obtain feedback on the study design and using this methodology to recruit patients. In response to the questionnaire, 72% of participants in this non-randomised study said they would participate in a randomised trial in which only half the participants were treated during the trial.

HEAT's biggest weakness was its failure to achieve the numbers of outcomes events needed for a robustly interpretable body of data. 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,[65] but we observed a rate of only 2.67/1000 person-years in the control group in the first 2.5 years of follow-up. There are a number of reasons for this. Fewer than anticipated suitable patients volunteered and proceeded to trial entry (16% of those approached). They were probably more health conscious than average: there was higher recruitment of those whose postcode indicated higher socioeconomic status compared to those from more deprived areas where prevalence of *H. pylori* infection was higher. This was a major factor contributing to the lower-than-expected overall prevalence of infection. By requiring a history of at least four aspirin prescriptions to ensure we were studying long-term users and excluding those already on antisecretory agents, we may have selected a low-risk population.

Finally, there is the issue of secular trends in peptic ulcer disease. ONS mortality data have shown a steady 2.5- to 3.4-fold reduction in deaths due to ulcers and their complications (with 1628 peptic ulcer deaths recorded in 2001 declining to 641 in 2019 and 531 in 2020) during this century.[99] To what extent these trends can be accounted for by the decline in *H. pylori* prevalence and better management of the use of NSAIDs and aspirin or whether ulcer disease is becoming an intrinsically milder condition is not clear. However, they are clearly important for the future approaches to this field.

Strengths and limitations

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 in chronically prescribed low-dose aspirin in primary care. Its size, the high follow-up rate for the primary outcome due to using primary care records, HES and ONS data, the very

low number of withdrawals and effective blinding will have substantially reduced potential sources of bias. Omitting mention of death due to peptic ulcer bleeding from the protocol was an error, but it did not affect the analysis, as there were no pre-hospitalisation deaths. 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 can neither 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 rather than new users, 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 Aspirin To Target Arterial Events in Chronic Kidney Disease (ATTACK) study.[100]

Health economics

While the HEAT study showed *H. pylori* eradication could reduce the incidence of peptic ulcer bleeding over 2.5 years, this economic analysis does not support the hypothesis that this would be cost saving, principally because the high numbers needed to treat make investment in prevention much more expensive than treatment of peptic ulcer bleeding in this population.

The low incidence of peptic ulcer bleeds and associated death rate, together with the relatively large number of individuals who did not require an overnight stay for it, suggests that the HEAT population presents a relatively low risk. However, the costs associated with hospital admission for peptic ulcer bleeding are broadly in line with estimates arising from the TRIGGER study of transfusion strategies.[80] In HEAT, hospital costs averaged just over £3500 in 2020–1 prices. In TRIGGER, the aggregate of in-hospital costs for acute UGIB averaged £2458 for initial hospitalisation and £391 for follow-up costs (2012–3 prices). In patients aged 75 and over (the nearest age demography to that of the HEAT participants), the estimated cost of initial hospitalisation was £3190. Other estimates have been higher, being for patients with prolonged ventilation in an intensive care unit or need for surgery.[75] Additional costs attributable to peptic ulcer bleeding can arise from possible use of ambulance services and use of hospital accident and emergency services, but these were not included due to data unavailability. In HEAT, the key driver of cost of care due to peptic ulcer bleeds was length of stay.

In the HEAT population, the infrequency of peptic ulcer bleeding and the non-response to invitations means that the costs of preventing one event with proactive screening is an order of magnitude greater than would be cost-effective, reflected by a negative-valued NMB, where both are the consequence of an inordinately high value for the NNT. This was consistent with a high health-related quality of life value estimated from the panel utility models for patients with bleeding; likely, reflecting patients consenting to the study were healthier than the general population. This contrasts with breath or stool testing and eradication therapy in patients with dyspepsia.[101] Dyspepsia was a contraindication to participation in HEAT, and new dyspepsia was uncommon during the study.

It is not surprising that none of the scenarios considered above becomes cost-effective. Arguably, eradication may be more relevant in populations with a much higher prevalence of *H. pylori*. However, the mode of presentation also differs geographically, although there is also an impetus to eradication where gastric cancer is the prime concern.[69] *H. pylori* eradication at the time of initiation of aspirin and test-and-treat approaches to aspirin users with dyspepsia may be the strategies most likely to be medically and economically viable.

Health economics and implications for clinical management

Our findings have the potential to 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) 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 where there is an increased risk of peptic ulceration and GI bleeding.[13–15]

An alternative view is that the decline in GI outcomes that has been detected by HEAT and the Hong Kong cohort study represents a research opportunity for the study of current issues rather than a threat to our ability to investigate old ones. In particular, at a time when there are data both favouring and repudiating beneficial effects of aspirin in cancer prevention and management, the background hazards of aspirin may be less than previously thought. Background levels of ulcer disease are declining. Add to that the availability of both *H. pylori* eradication and acid suppression as prophylaxis, and arguably, there is scope for a more liberal use of aspirin in the search for a silver salicylate anticancer bullet.[102]

Chapter 8 Conclusions and future studies

We have shown a benefit from *H. pylori* eradication in a population spread widely across the UK, particularly in England and Wales. Clinical trials tend to attract health-conscious patients. The epidemiological sequel to HEAT that we are conducting will help to understand whether this played a significant part in the lower-than-expected ulcer bleeding rates we saw. The protection against ulcer bleeding that we observed was modest compared to studies of PPI coprescription. However, there is a limited appetite for long-term PPI prescribing both generally and in the context of aspirin use.[17] A study that showed a bigger effect than we did would be influential. The most obvious way to take this forward would be to study the effect of *H. pylori* eradication in patients starting aspirin for the first time, when event rates are high and may include a population of susceptible patients lost to a study like HEAT by a process of prior attrition. In addition, for such a strategy to compete with PPI prophylaxis, it would be important to reinvestigate the phenomenon of late loss of protection and if it is reconfirmed as a significant effect to identify mitigating strategies. These would probably involve mechanistic studies of gastric mucosal inflammation.

Context is important in determining the overall value of this approach. Currently, *H. pylori* prevalence is low in Westernised societies. Management via *H. pylori* eradication would be more relevant in countries where prevalence of infection is higher. It is not clear whether *H. pylori* will vanish or persist at low levels in Westernised societies. If it is the latter, the association between *H. pylori* is so strong that most (of a dwindling number of) cases would still be prevented.

The apparent reduction in GI cancer deaths with *H. pylori* should be further investigated to see if the finding can be confirmed. This could be done in any further trial of the effect of eradication on ulcer bleeding. However, as indicated above, such a trial may not be of sufficiently high priority to get done. An alternative approach would be to do nested case–control studies of incident cancers and cancer deaths in subjects enrolled in aspirin anticancer trials.

There are two possible hypotheses that could be tested: that in the presence of aspirin, *H. pylori* promotes cancer or that it advances death in patients who have already got cancer. The latter is arguably the more likely in view of the long lead time for cancer development.

In patients that have already died, stored tissue could be used for histological and molecular approaches to establishing their *H. pylori* status retrospectively.

Chapter 9 Equality, diversity and inclusion

Helicobacter Eradication Aspirin Trial completed recruitment prior to publication of the INCLUDE framework and guidance, so we did not have a formal policy that relates to that document. Nevertheless, we feel our study was in line with the principles of INCLUDE. Investigators were implicitly committed to treating all people equally and with respect, irrespective of their age, disability, race, religion or belief, or their gender, marital or sexual status. We would point to several aspects of the study in support of this.

Preparation

A significant proportion of the pilot study we carried out in preparation for HEAT related to patient preferences. During the pilot study, we sought the views of over 2000 patients from the north and south of England and the Midlands on the acceptability of the trial design, breath testing and eradication treatment.

Recruitment

The initial step in patient recruitment was, by definition, inclusive and blind to differences in age, sex or deprivation. Virtually, all subjects over the age of 60 who were on aspirin were written to and had a chance to participate in the study. We only studied patients who were 60 years old or greater. It is well recognised that ulcer complications increase exponentially above this age. There were more men than women in the study. This similarly reflects the distribution of ulcer disease and the complication of bleeding.

Diversity and deprivation

Because only a proportion of patients took up the invitation to participate in the trial, there was a danger that we would enrol individuals that were more health conscious or who suffered a lower level of deprivation than average or representative of the overall population at risk. Because deprivation is the context for a high prevalence of *H. pylori* infection and ulcer disease, we had an informal policy of targeting practices with a postcode associated with higher deprivation.

Results in context

We are currently conducting an epidemiological study across all practices that contributed relevant data to evaluate how successful we were in our efforts to study patients who were representative of the population from whence they came.

Structures

We were advised by two lay representatives on patient communications, information and consent literature, one of whom was a member of the steering committee for the whole of the trial.

Research team

We did not have a formal gender equality policy but appointed on merit. There were 36 authors on the main results paper, of whom 21 were male and 15 were female. The primary writing group were 50% female. The trial co-ordinator and her assistant were both female.

Additional information

CRediT contribution statement

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Other contributions

HEAT trialists: Investigation, Validation.

Collaborators on the preparatory pilot studies, funded by the Medical Research Council: Funding acquisition.

Acknowledgements

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Ward (lay representative), Angela Shone (sponsor representative, University of Nottingham), Jennifer Dumbleton (University of Nottingham), Professor Chris Hawkey (University of Nottingham), Professor Richard Hobbs (University of Oxford), Prof Denise Kendrick (University of Nottingham).

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Trial pharmacist: Sheila Hodgson (Nottingham).

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The trial was undertaken in accordance with International Conference on Harmonisation guidelines and the Declaration of Helsinki and was approved by East Midlands, Leicester Central Research Ethics Committee (REC 11/EM/0434) and the MHRA (CTA Ref 03057/0052/001-0001) in December 2011. The TSC was constituted according to NIHR guidelines and delegated day-to-day management to a project management group, organised by the trial manager under the direction of the trial chief investigator. The trial was also overseen by a three-person IDMC which had access to partially unblinded (Group A and Group B) data. All participants signed an Informed Consent Form approved by the REC prior to any trial procedures. The trial was registered at clinicaltrials.gov (ID NCT01506986)

Information governance statement

The University of Nottingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under Data Protection legislation

the University of Nottingham is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for DHSC's Data Protection Officer here (www.nottingham.ac.uk/utilities/privacy/privacy-information-for-research-participants.aspx).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/LLKF7871.

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Publications

Publications and conference papers arising from this study

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