NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

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

[1]Simple Trials for Academic Research Unit, School of Medicine, University of Nottingham, Nottingham, UK
[2]Centre for Academic Primary Care, School of Medicine, University of Nottingham, Nottingham, UK
[3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[4]Primary Care Research Centre, University of Southampton, Southampton, UK
[5]TCR Nottingham Ltd, Langley Mill, UK
[6]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[7]Aberystwyth Business School, Aberystwyth University, Aberystwyth, UK

[*]Corresponding author cj.hawkey@nottingham.ac.uk

Published August 2025
DOI: 10.3310/LLKF7871

Scientific summary

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

Health Technology Assessment 2025; Vol. 29: No. 42
DOI: 10.3310/LLKF7871

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 09/55/52) and is published in full in *Health Technology Assessment*; Vol. 29, No. 42. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 4

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 4 and is ranked 30th (out of 174 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number 09/55/52. The contractual start date was in March 2012. The draft manuscript began editorial review in August 2023 and was accepted for publication in February 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).