



HELicobacter Pylori screening to prevent gastrointestinal bleeding in patients with acute Myocardial Infarction (HELP-MI SWEDEHEART) - Design and rationale of a cluster randomized, crossover, registry-based clinical trial

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ABSTRACT

Background The role of *Helicobacter pylori* (*H. pylori*) screening and eradication on reducing upper gastrointestinal bleeding (UGIB) complications after acute myocardial infarction (MI) is uncertain. The HELicobacter pylori screening to prevent gastrointestinal bleeding in patients with acute MI (HELP-MI SWEDEHEART) trial aims to determine whether systematic *H. pylori* screening compared to usual care reduces UGIB, mortality, and cardiovascular outcomes after MI.

Methods A cluster randomized, crossover, registry-based clinical trial using SWEDEHEART as trial platform for study population definition and source for data collection in combination with nationwide Swedish health data registries. Thirty-five Swedish hospitals, organized into 18 clusters based on percutaneous coronary intervention networks, were randomized to either routine *H. pylori* screening for adults with acute type-1 MI or usual care. After 1 year, a 2-month blanking period was followed by a crossover to the alternate allocation for 1 year. The trial enrolment was concluded after one additional year of registry-based follow-up. The primary endpoint is UGIB. Secondary endpoints include all-cause death, cardiovascular death, readmission for MI, stroke, or heart failure. Endpoints will be reported combined (Net Adverse Clinical Events; Major Adverse Cardiac or Cerebrovascular Events) and separately. The primary analysis will include all available follow-up time corresponding to a maximum follow-up time of 3 years and 2 months.

Conclusion HELP-MI SWEDEHEART aims to determine the utility of routine *H. pylori* screening to reduce UGIB and improve cardiovascular outcomes after MI. By integrating national registry follow-up data with a pragmatic trial design, it has the potential to provide evidence for the effect of the implementation of routine *H. pylori* screening as part of acute MI care.

Trial Registration ClinicalTrials.gov, NCT05024864. (Am Heart J 2025;286:66–74.)

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Background

The adoption of evidence-based therapies, particularly the use of potent antithrombotic treatments, has significantly reduced the incidence of recurrent ischemic events in patients with acute myocardial infarction (MI) over the past decades.¹ However, this progress has come at a cost; an increased risk of bleeding, in particular from the upper gastrointestinal tract.^{2, 3} Upper gastrointestinal bleeding (UGIB) is not only a direct cause of increased morbidity, mortality, and medical care costs but may also lead to a higher risk of recurrent cardiovascular events due to discontinuation of antithrombotic drugs.⁴

Optimizing the balance between preventing thrombotic events and the risk of bleeding requires careful management of risk factors. In addition to established risk factors, chronic gastric infection with *Helicobacter pylori* (*H. pylori*) may represent an overlooked modifiable risk factor for UGIB after MI.⁵ Observational studies support an increased UGIB risk in cardiology when *H. pylori* infection coincides with antithrombotic therapy.⁶ Furthermore, chronic inflammation associated with *H. pylori* infection might contribute to the progression of atherosclerosis, plaque rupture, and ultimately, incident MI.⁷

Despite the lack of data derived from randomized clinical trials, *H. pylori* screening and eradication are recommended by expert consensus in gastroenterology guidelines for chronic use of aspirin or nonsteroidal anti-inflammatory drug therapy^{8, 9} but are not considered in current cardiology guidelines¹⁰⁻¹² and practice.¹³ The European and American Societies of Cardiology recommend proton pump inhibitors (PPIs) in patients with higher-than-average risk of gastrointestinal bleeding.^{11, 12, 14} However, the net benefit of long-term PPI treatment is unknown. In observational studies, long-term PPI treatment has been associated with higher rates of cardiovascular events,¹⁵ but also chest infections,¹⁶ dementia,¹⁷ and chronic kidney disease.^{18, 19}

Results from the recent randomized controlled Helicobacter Eradication Aspirin Trial (HEAT) demonstrated a reduction in UGIB through systematic *H. pylori* eradication in individuals taking low-dose aspirin who tested positive for *H. pylori*. However, the event rate was lower than expected, and the observed effect was only transient, diminishing after 2.5 years of follow-up.²⁰ This underscores the need for further studies to identify the optimal target population and timing for implementing a routine *H. pylori* screening strategy to prevent UGIB in individuals on antiplatelet therapy.^{5, 21}

In summary, the utility of *H. pylori* as a risk factor for UGIB and recurrent cardiovascular events in patients with MI on potent antithrombotic medication remains uncertain. Therefore, we are conducting a randomized trial to determine the utility of routine *H. pylori* screen-

ing to reduce UGIB and improve cardiovascular outcomes in this high-risk population after MI.

Methods/Design

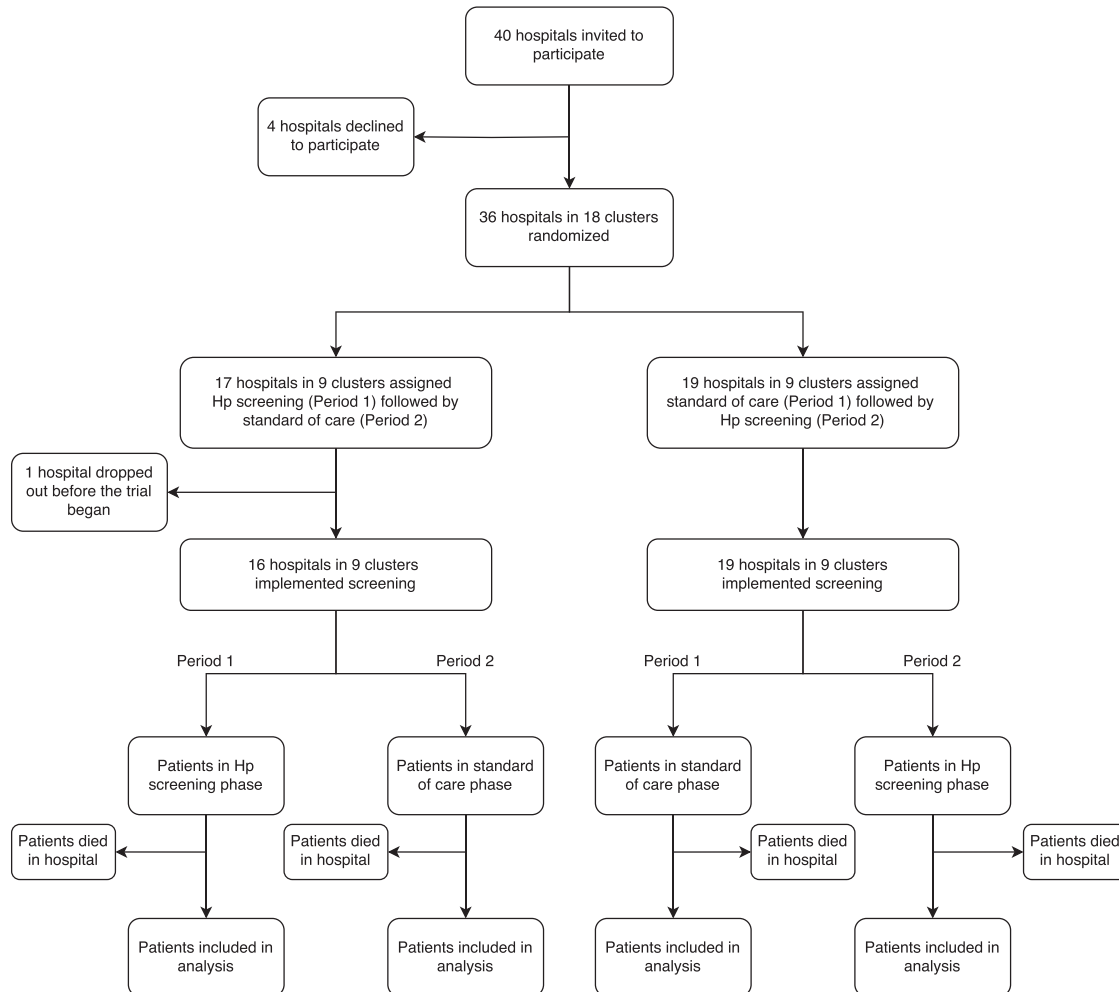
Study design and objectives

HELP-MI SWEDEHEART (*HELICobacter pylori* screening to prevent gastrointestinal bleeding in myocardial infarction [NCT05024864] Swedish Web system for enhancement and development of evidence based care in heart disease evaluated according to recommended therapies²²) is a prospective, open-label, cross-sectional 2-period (each 1 year) 2-sequence cluster randomized crossover (CRXO), registry-based, clinical trial (RRCT) designed to evaluate the effectiveness of routine *H. pylori* screening to reduce UGIB complications after acute MI. The primary objective of HELP-MI SWEDEHEART is to determine whether systematic *H. pylori* screening significantly reduces the incidence of UGIB after acute MI. Secondary objectives assess whether systematic screening for *H. pylori* significantly reduces all-cause death or cardiovascular outcomes. The hypothesis is that *H. pylori* infection is a causal and reversible factor contributing to post-MI UGIB. It is anticipated that *H. pylori* diagnosis and eradication in patients with MI who test positive could reduce UGIB risk, enhance adherence to secondary prevention, and improve cardiovascular outcomes. In addition, health economic assessment of routine *H. pylori* screening during hospitalization for acute MI will be performed using cost-effectiveness modeling and evaluate functional status including health-related quality of life (HRQoL).

Study population

All patients admitted at a study site during the study periods with a diagnosis of type-1 MI and registered in SWEDEHEART were included.

The 40 largest hospitals in Sweden providing acute coronary care were invited to participate. To reduce the risk of crossover of individuals from participating hospitals randomized to different trial periods (cluster period contamination), trial sites were distributed into 18 clusters based on percutaneous coronary intervention networks before the randomization was performed by an independent statistician. The clusters were allocated 1:1 to *H. pylori* screening followed by no *H. pylori* screening, or no *H. pylori* screening followed by *H. pylori* screening, using a single computer-generated randomly permuted block, ensuring no more than one additional hospital in either treatment sequence. Each study period lasted one year. *H. pylori* analyzer units were only available in the hospitals during the *H. pylori* screening period and were then relocated (Figure 1).

Figure 1. Study flow chart.

Intervention and control group

The intervention was routine *H. pylori* screening of all patients with type-1 MI at hospitals within clusters randomized to screening. *H. pylori* infection was diagnosed using a bedside ¹³C-urea breath test (UBT) as a part of MI routine care during the hospitalization period (details in appendix). All patients hospitalized at participating departments in clusters with screening received information, whereas decisions based on the *H. pylori* screening result were individually taken and communicated by the caring physician. All *H. pylori* analysis equipment was supplied by the study organizers, and all centers used the same equipment (Kibion® Diabact®, Mayoly Spindler, Chatou, France).

For patients testing *H. pylori* positive, eradication therapy was prescribed at the caring physician's discretion.

The individual implementation of *H. pylori* screening, test result, and eradication therapy prescription were recorded in SWEDEHEART²² (details in appendix), allowing a secondary as-treated analysis. Control of successful *H. pylori* eradication therapy with either UBT or *H. pylori*-antigen in feces 6 weeks after completed eradication therapy was recommended to the treating physician but not centrally followed up.

To assess the adherence to *H. pylori* screening clusters during screening periods, an online survey was sent out to participating sites to assess reasons for the failure of routine *H. pylori* screening (details in appendix) after the screening period was completed.

At hospitals within clusters randomized to no screening, all MI patients received usual care without routine *H. pylori* screening and were followed in national registries

as described below. During the period without *H. pylori* screening, the study's UBT equipment was not available, thus limiting a potential carryover effect.

Power calculations

From an existing database encompassing 84 090 patients with acute MI between 2012 and 2016 (SWEDHEART merged with the National Patient Registry)²³ we found severe UGIB after MI to occur in 2.5% and increasing up to 4% in elderly patients during a median follow-up of 2 years in line with follow-up time for the planned trial. From the same population, we have subsequently reported an incidence rate of severe UGIB of 1.5% after 1-year follow-up.² Based on the HELP-MI SWEDHEART pilot study, the prevalence of an active *H. pylori* infection in a contemporary MI cohort was found to be around 20%.²⁴ Assuming that *H. pylori* infection in combination with antithrombotic therapy yields at least a 3-fold increased bleeding risk,⁸ and that screening of *H. pylori*, assuming subsequent eradication in the case of a positive result, reduces this risk to the same level as in uninfected patients, we anticipate at least a 30% relative risk reduction in the group screened for *H. pylori*. The anticipated effect size of a hazard ratio of 0.70 was based on consensus in the steering group including gastroenterologists and cardiologists. Data were simulated using the proposed cluster-randomized crossover study design with 2 years of patient inclusion followed by an extra year of follow-up. Simulation of cluster randomization to screening during either the first or the second period was performed on data from the originally planned 36 participating hospitals in the database with a total of 11,544 screened and 11,544 control patients (based on admission rates for 2016) included uniformly so that the distribution of age and hospital size was preserved. For each patient, an event time for UGIB was simulated separately using a Weibull distribution to account for the fact that the risk seems to be the largest closest to the index MI and decreases thereafter. All parameters were estimated from the study database and each simulated data set was analyzed using the proposed cluster-summary method. Given the assumptions outlined above, the simulation of the primary analysis using 1-2 years of follow-up yielded an 87% power to detect a hazard ratio of 0.70 when comparing screening with no screening.

Outcomes

All clusters will be analyzed as randomized, irrespective of whether individual patients underwent screening, in accordance with the intention-to-treat (ITT) principle. All endpoints in HELP-MI SWEDHEART are summarized in Figure 2 and listed in detail in Supplementary Table 1.

The primary endpoint is UGIB defined by the appearance of ICD codes obtained from the mandatory National Patient Register including ICD codes from all in-patient

and specialized outpatient visits in Sweden,²⁵ previously found to have a high validity for gastrointestinal bleeding events (sensitivity 82.3%, specificity 99.3%, positive predictive value 98.1%, negative predictive value 93.1%).²⁶ No central adjudication of events will be performed.

Secondary endpoints are all-cause and cardiovascular mortality, rehospitalization with MI, hospitalization with stroke or heart failure, and UGIB requiring blood transfusion. Secondary endpoints will be reported individually and as composite endpoints (1. Net Adverse Clinical Events [NACE]: All-cause death, UGIB, rehospitalization with MI, or stroke; 2. Major Adverse Cardiac or Cerebrovascular Events [MACCE]: Cardiovascular death, rehospitalization with MI, or hospitalization for stroke) to include clinically most important outcomes and increase statistical power.

MI during the initial hospital stay and readmission due to a nonfatal MI during the first month will not be centrally adjudicated but were established by the treating cardiologist, and directly registered in SWEDHEART. The registry provides instructions on how to define a Type 1 MI following the 4th Universal Definition of Myocardial Infarction,²⁷ and the validity of MI diagnoses compared to health registries is high.²² After day 31, rehospitalization for MI will be captured in the National Patient Register.

All-cause death will be obtained from the Swedish Population Register, including the vital and emigration status of all Swedish residents,²⁸ and the National Cause of Death Register which is a high quality virtually complete nationwide register of all deaths in Sweden since 1952.²⁹

Cardiovascular death as the primary cause of death will be obtained from the National Cause of Death Register. Hospitalization for heart failure and stroke will be obtained from the National Patient Register.²⁵

UGIB requiring blood transfusion will be obtained from the Scandinavian Donations and Transfusions (SCANDAT) database which has complete coverage of blood transfusions in Sweden.³⁰

All ICD codes for the above-mentioned diagnoses are summarized in Supplementary Table 2.

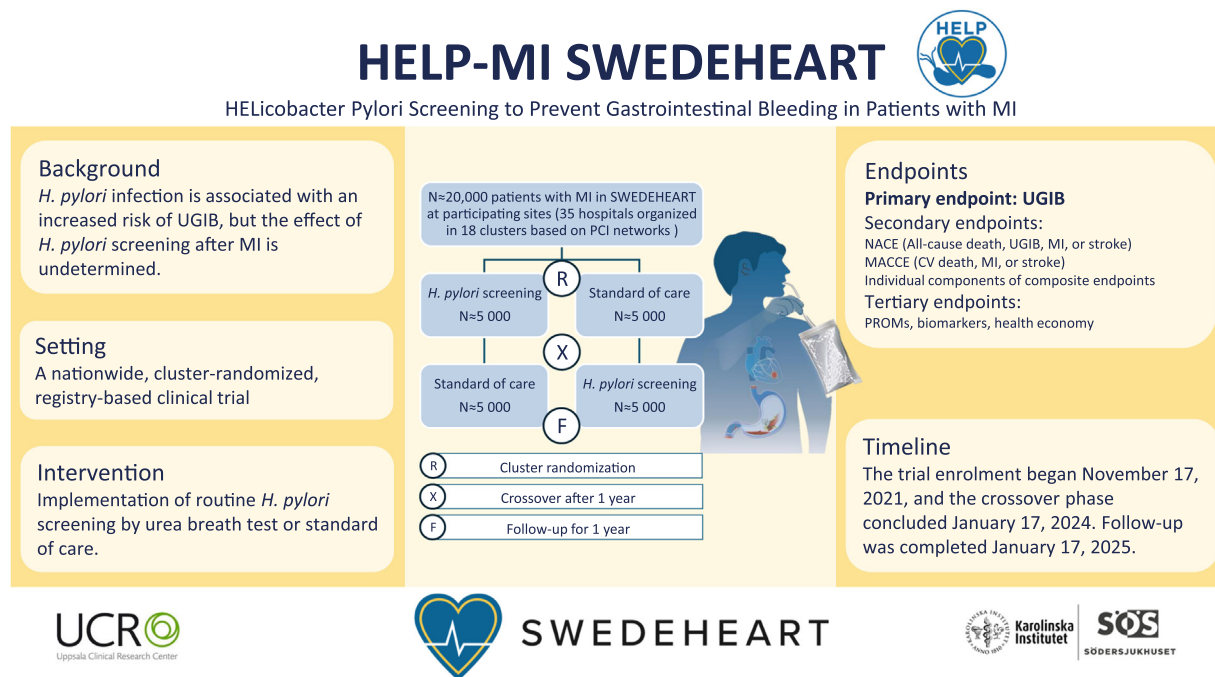
Tertiary endpoints include symptoms, HRQoL, health economy, and changes in blood glucose and blood lipids during follow-up (details available in appendix).

Health economics based on cost-effectiveness analysis will be performed after one year and include long-term modeling.

Multiple prespecified subgroup analyses will be performed as well as secondary per-protocol and as-treated analyses (appendix for details).

The linkage with the National Patient Registry, the National Cause of Death Registry, the National Prescribed Drug Registry (prescribed and dispensed treatments),³¹ and Statistics Sweden (socioeconomic data) will be done at the end of follow-up.

Figure 2. UGIB denotes upper gastrointestinal bleeding; NACE, net adverse clinical events; MAE, major adverse event; MACCE, major adverse cardiovascular or cerebrovascular event; CV, cardiovascular; MI, myocardial infarction; PROM, patient reported outcome measures.



Ethical approval

HELP-MI SWEDEHEART is an investigator-initiated trial conducted under the Declaration of Helsinki, approved by the Swedish Ethical Review Authority (2020-01885, 2024-03095-02). The intervention consisted of a noninvasive *H. pylori* diagnostic strategy with minimal to negligible risk to individuals in participating clusters. Since allocation to *H. pylori* screening was carried out in clusters, and not at an individual level, informed consent for randomization was waived. Individual consent to carry out the *H. pylori* screening test was obtained in clinical practice but without study-specific documentation. Since the treatment of *H. pylori* infection was at the discretion of the caring physician to prescribe medications according to current treatment recommendations, the trial protocol intervention includes only the diagnostic strategy. As the HELP-MI SWEDEHEART trial implements a well-established noninvasive diagnostic test in clinical post-MI routine, no study-specific safety assessment was performed. The group randomized to care without *H. pylori* screening received usual care according to clinical practice. No intervention took place, and no study-specific contact was made with the individuals.

All patients hospitalized at participating clusters were informed about data collection and their right to opt-out. The *H. pylori* screening test result and treatment were registered in SWEDEHEART. All data linkages were

granted and performed by the National Board of Health and Welfare and Statistics Sweden.

Statistical analyses

All enrolled patients discharged alive will be included in the primary ITT analyses. Secondary per-protocol and as-treated analyses will be performed at a later stage. Numerical variables will be presented in terms of mean and standard deviation, and also as median and quartiles. Categorical variables will be presented as counts and percentages. The primary and secondary endpoints are time-to-event endpoints (Supplementary Table 1). Patients will be censored for death if not part of the event. The primary analysis will include all available follow-up time, which ended on January 17, 2025. This corresponds to a maximum follow-up time of 3 years 2 months, and a minimum of 1 year. Other follow-up times will be analyzed in sensitivity and supplementary analyses (see appendix).

For each endpoint, the number of events, total person-time (time until event or censoring), and incidence rate (number of events per person-time) will be presented in tables. This will be done per cluster-period, and also per trial arm (screening/no screening). In addition, cumulative hazard plots will be presented with one curve for each trial arm. The primary analysis is a cluster-summary analysis. Next, a negative binomial model will

be fitted with the number of events as the dependent variable, and intervention (screening/no screening), period (first/second), and cluster as fixed independent variables. In addition, the logarithm of the total cluster-period person-time will be added as an offset. The results will be presented as a rate ratio for screening with a 95% confidence interval (CI) and a 2-sided *P*-value for the null hypothesis of no screening effect. In a secondary sensitivity analysis, the outcome will be analyzed using Cox proportional hazards models. These models will include cluster and cluster-period as gamma-distributed random effects. The models will be fitted both without further adjustment and with adjustment for sex and age. The results will be presented as hazard ratios with 95% CIs and *P*-values for the null hypothesis of no treatment effect. The primary analysis (cluster summary using all follow-up time) of the primary and secondary endpoints will be adjusted for multiplicity using a hierarchical strategy, ordering the endpoints according to Supplementary Table 1.

Prespecified subgroup analysis to determine the heterogeneity of treatment effect will be performed (details in the appendix, including Supplementary Tables 3 and 4) but not all included in the primary report. Analyses of tertiary endpoints encompassing individuals <80 years of age who participated in the SWEDEHEART follow-up are also described in the online appendix.

A detailed statistical analysis plan with prespecified analyses will be published alongside the primary report.

Study organization and data safety monitoring board

Karolinska Institutet, Stockholm, Sweden, is the sponsor of this investigator-initiated trial. The steering group consists of experts from 10 centers across Sweden, including cardiologists and gastroenterologists. Uppsala Clinical Research Center, Uppsala University, Sweden provides project and data management, and statistical support. No data safety monitoring board has been appointed.

Timelines

Clusters were randomized on July 30, 2021. Study enrolment for phase 1 started on November 17, 2021. Crossover to the opposite strategy occurred one year later, on November 17, 2022, followed by a blanking period for device installation and site initiation. Active *H. pylori* screening in phase 2 started on January 17, 2023, and was completed on January 17, 2024, finalizing enrolment. The follow-up phase continued until January 17, 2025, which was the date for study closure. To account for a delay in reporting data to the National Board of Health and Welfare, SWEDEHEART data will be merged with the other nationwide Swedish health data registries after April 17, 2025.

Discussion

The HELP-MI SWEDEHEART trial aims to determine whether routine screening for *H. pylori* in patients following MI can prevent UGIB, improve CV outcomes and overall prognosis. Given the increasing incidence of adverse bleeding events and worse associated cardiovascular outcomes in MI patients,² and the increasing focus on optimizing the ischemia-bleeding balance,¹² this trial is anticipated to provide valuable evidence on the role of *H. pylori* as a modifiable risk factor for UGIB complications post-MI.

To assess the prevalence of active *H. pylori* infection in a contemporary MI cohort and to evaluate the feasibility of incorporating *H. pylori* diagnostics into routine MI care, we performed a multicenter prospective pilot study of 310 consecutive MI patients, and could show that active *H. pylori* diagnosed by bedside UBT was prevalent in 20% of the patients,²⁴ about twice as common as in the overall Swedish population.³² Importantly, *H. pylori* screening was feasible in clinical routine during MI hospitalization. Furthermore, smoking, lack of PPI use, and ST-elevation MI were more common in patients with MI testing positive for *H. pylori*. After censoring patients with concurrent PPI use, *H. pylori* prevalence increased to 24%. Overall, 34% of patients were PPI treated,²⁴ which is in line with data from similar healthcare settings.¹⁹ Prespecified subgroup analyses of individuals with or without concomitant PPI treatment before enrolment as well as after discharge are planned to assess this aspect.

The numbers from the latter study position Sweden at the lower end of the global *H. pylori* infection prevalence, which is substantially higher in for example Africa, Asia, and South America.³³

The HEAT study reported an active *H. pylori* infection in 18% of 30,166 British individuals,²⁰ in line with the results from our pilot study.²⁴ These findings reinforce *H. pylori* as a common risk factor for bleeding complications from cardiovascular preventive actions. The HEAT investigators demonstrated for the first time a significant reduction in UGIB by routine *H. pylori* screening and eradication.²⁰ However, due to several limitations and study-specific aspects, the interpretation of the trial results and the application of the *H. pylori* test-and-treat strategy to clinical practice remain controversial.^{5, 21} In particular, the loss of bleeding protection beyond 2.5 years of follow-up remains unclear. One important contributing reason to this finding may be the overall low-risk population enrolled in the trial: only long-term low-dose aspirin users were eligible which excluded individuals newly initiated on aspirin who likely have the highest risk of bleeding.³⁴ This aspect was reflected in the lower-than-expected bleeding event rate which led to the early termination of the trial. Moreover, only a negligible number of patients were on dual antithrombotic therapy commonly used in secondary prevention strategies after

cardiovascular events. Targeting patients with a strong indication for potent antiplatelet therapy but also a higher risk of UGIB may optimize the risk-benefit ratio of a routine *H. pylori* screening approach.

Whereas HEAT addressed the efficacy of *H. pylori* eradication in unselected, chronic aspirin users in primary care, HELP-MI SWEDEHEART aims to determine the effectiveness of routine *H. pylori* screening to reduce UGIB and cardiovascular complications after acute MI on potent antithrombotic medication. By using a pragmatic, cluster-randomized design with registry-based follow-up performed as part of routine clinical practice, we anticipate a study population close to the underlying population, and thus, generalizable results. Furthermore, effects on secondary cardiovascular outcomes and death as well as tertiary outcomes, such as symptoms and quality of life measurements, will contribute to the interpretation of the results. Finally, health economic assessments are scheduled to inform stakeholders and policy makers.

Beyond the scope of the trial, HELP-MI SWEDEHEART will fuel the recently raised notion of “gastro-cardiology”, in which *H. pylori* infection in addition to bleeding risks possibly contributes to residual CV risk from chronic systemic inflammation.³⁵ The reverse association, *e.g.* increased MI risk after GI bleeding has also received attention for its consequences for the clinical presentation, comorbidities, invasive revascularization strategies, and post-MI prognosis³⁶ as well as tailoring of antithrombotic therapy in CVD with gastrointestinal comorbidities.^{37,38}

Conclusion

HELP-MI SWEDEHEART aims to add important evidence regarding the potential implementation of routine *H. pylori* screening to reduce UGIB complications and improve cardiovascular outcomes after MI.

Funding

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Conflict of interest

RH reports lecture and consulting fees to institution from AstraZeneca, Pfizer and BMS. SJ reports institutional research grants from Astra Zeneca, Jansen, Amgen, MSD, Novartis, Elixir inc., Novartis, Novo Nordisk. OF reports consulting fees from GSK and MSD and speaker fees from Sanofi Pasteur. OA reports research grants from Astra Zeneca and Abbott Vascular and speaker fees from Boston Scientific, Medtronic, Abbott Medical

and Meril Life. PMH reports consulting fees to Uppsala University from Milltons Ltd, Cambridge, UK. JA reports speaker and consulting fees from Novartis, Orion Pharma, Boehringer Ingelheim and Astra Zeneca. DE reports advisory board/speaker fees from Amgen, AstraZeneca, Chiesi, Sanofi, NovoNordisk, InfraredX/Nipro and Kaminari Medical. JL reports advisory boards fees from Chiesi and Bayer. TJ reports research grants and consulting fee to institution from MSD and Amgen, respectively. MB reports speaker and consultant fees to institution from Amarin, Amgen, Heel, Novartis, and Fresenius Kabi.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ahj.2025.03.014](https://doi.org/10.1016/j.ahj.2025.03.014).

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tualization. **Magnus Bäck:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

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