Helicobacter Pylori Screening after Acute Myocardial Infarction

The Cluster Randomized Crossover HELP-MI-SWEDEHEART Trial

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Declaration of interest

- Research contracts : Institutional grants from the Swedish Heart Lung Foundation and Region Stockholm.
- Consulting/Royalties/Owner/ Stockholder of a healthcare company : Institutional lecture and advisory board fees from MSD/Pfizer and AstraZeneca

Declaration of interest

Unrestricted grants to fund the HELP-MI SWEDEHEART trial from

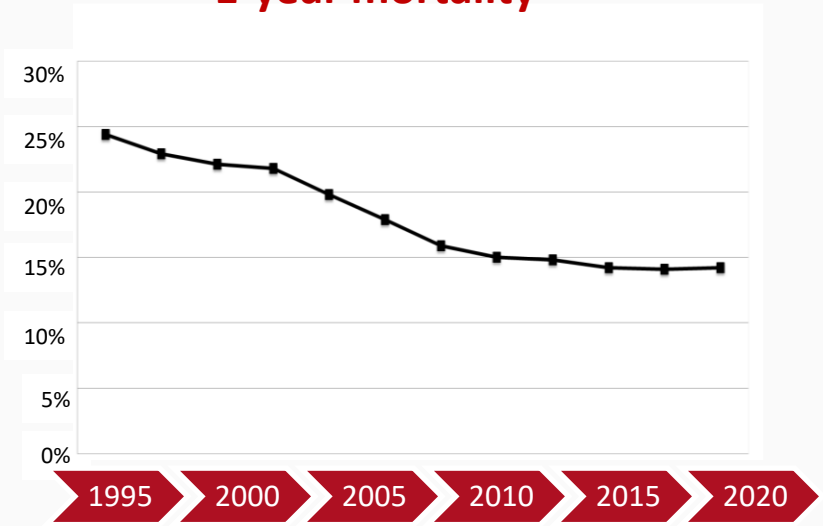
- The Swedish Heart-Lung Foundation
- The Swedish Research Council
- Region Stockholm

➢No funding from industry or for-profit organizations

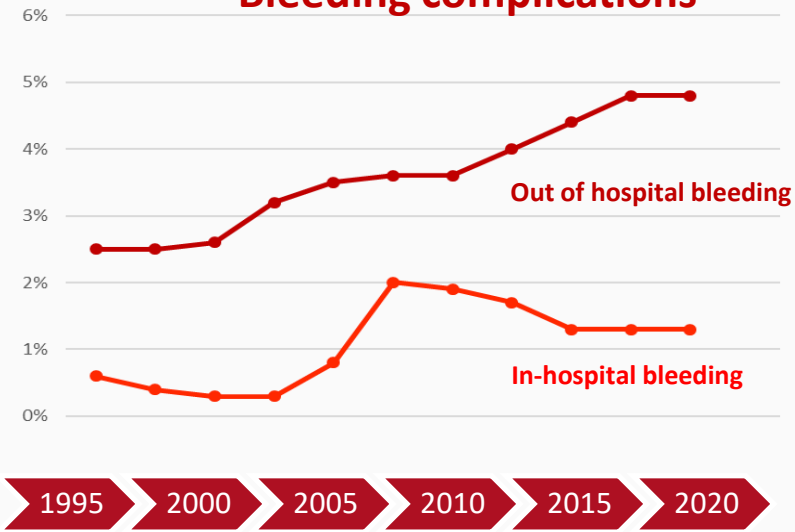
Background

Prognosis post MI - Balance of ischemia and bleeding

1-year mortality



Bleeding complications



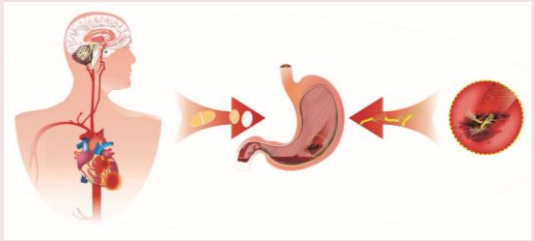
Simonsson M, et al. Temporal trends in bleeding events in acute myocardial infarction: insights from the SWEDEHEART registry. European heart journal 2020 41;7 833-843

HELP-MI SWEDEHEART

Setting

A nationwide, cluster randomized, crossover, registry-based clinical trial

Background



Aim and Intervention

To investigate, in a real-world setting, the effectiveness of adding routine *H pylori* screening by urea breath test to usual care on upper gastrointestinal bleeding (UGIB) after acute myocardial infarction.

N=18,466 patients with MI in SWEDEHEART at participating sites (35 hospitals from 18 PCI networks/clusters)

R

H pylori screening N=4,905

Usual care N=4,659

X

Usual care N=4,562

H pylori screening N=4,341

F

R Cluster randomization

X Crossover after 1 year

F Follow-up for 1 year

Endpoints

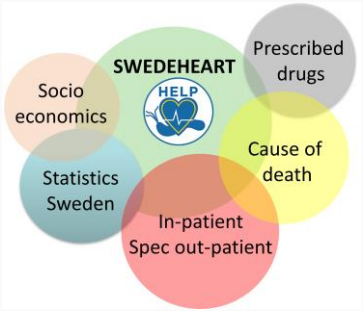
Primary endpoint: UGIB

Secondary endpoints:

NACE (All-cause death, UGIB, MI, or stroke)

MACCE (CV death, MI, or stroke)

Individual components of composite endpoints in the primary **intention-to treat** and secondary **per-protocol** populations.



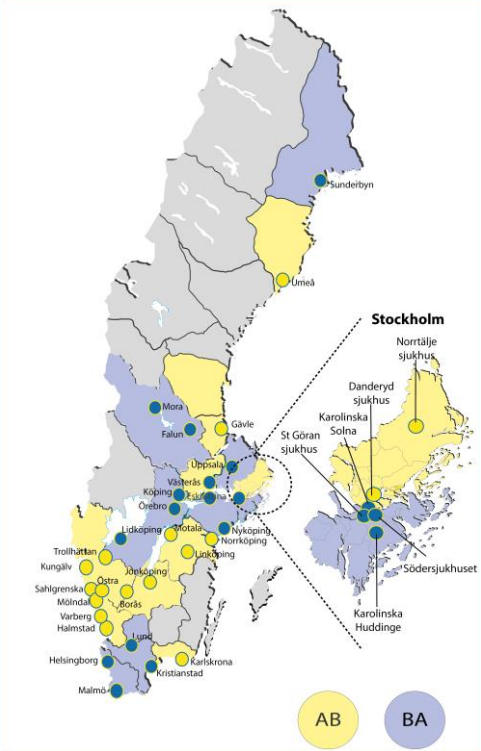
UCR Uppsala Clinical Research Center

SWEDEHEART

Karolinska Institutet

SÖS SÖDERSJUKHUSET

HELP-MI SWEDEHEART



Inclusion criteria

1. Age ≥ 18 years at admission
2. Registration with a Swedish personal identity number
3. Type 1 MI discharged alive and registered in SWEDEHEART during the study period

Exclusion criteria

1. Not applicable

Statistics

- The primary **intention-to-treat** analysis was a cluster-summary analysis using a negative binominal model.
- The results are presented as a rate ratio for screening with a 95% confidence interval and a two-sided p-value for the null hypothesis of no screening effect.
- The primary analysis used all follow-up time of the primary and secondary end points (Median follow-up time of 1.9 years (min-max 1-3.2 years) and was adjusted for multiplicity using a hierarchical strategy.
- **Per-protocol** analyses encompass patients with conclusive *H pylori* screening result using instrumental variable methods, based on flexible proportional hazards model.

Sample Size Estimation

Based on a nationwide observational study and a pilot study in a contemporary MI population, we anticipated

Sarajlic P, et al. Eur Heart J Cardiovasc Pharmacother. 2022;8(5):483-491.
Warme J, et al. American heart journal. 2021;231:105-109.

- 20% prevalence of active *H pylori* infection
- 2.5% upper gastrointestinal bleeding rate over an average follow-up of 2 years
- 30% relative risk reduction of screening for *H pylori*

➢ a simulation based on historical data encompassing 11,544 screened and 11,544 usual care patients with MI using analyses similar to the present trial yielded an 87% power to detect a rate ratio of 0.7 when comparing screening with no screening, at a two-sided alpha=.05.

Characteristics of the Patients

Characteristic	No. (%) of patients	
	Helicobacter pylori screening (n = 9245)	Usual care (n = 9221)
Demographics		
Age, median (IQR), y	71 (61.0-79)	71 (62-79)
Sex		
Female	2636 (28.5)	2692 (29.2)
Male	6609 (71.5)	6529 (70.8)
Risk factors		
Hypertension	6384 (69.1)	6401 (69.4)
Diabetes	2472 (26.7)	2416 (26.2)
Previous cardiovascular disease		
Myocardial infarction	3124 (33.8)	3012 (32.7)
Percutaneous coronary intervention	2529 (27.4)	2467 (26.8)
Medication at admission		
Aspirin	2360 (26.2)	2340 (26.0)
Proton pump inhibitor	2284 (24.7)	2275 (24.7)
Direct oral anticoagulation	862 (9.6)	909 (10.1)

Characteristics of the Patients

Characteristic	No. (%) of patients: *Helicobacter pylori* screening (n = 9245)	Usual care (n = 9221)
Anemia at admission, No. (%)		
No anemia (hemoglobin ≥120 g/L)	7532 (85.6)	7535 (86.4)
Mild anemia (hemoglobin 100-120 g/L)	1052 (12.0)	1006 (11.5)
Moderate to severe anemia (hemoglobin <100 g/L)	213 (2.4)	181 (2.1)
Kidney failure at admission (eGFR<60 mL/min/1.73m^2)	2222 (24.1)	2181 (23.7)
In-hospital course		
Helicobacter pylori		
Screened	6480 (70.1)	0
Tested positive	1532 (16.6)	
Eradication prescribed	1481 (16.0)	
Revascularization	7748 (83.8)	7732 (83.9)
ST-segment elevation myocardial infarction	3400 (36.8)	3488 (37.8)
Median duration of hospital stay, d	4 (3-6)	4 (3-6)

H pylori prevalence: 23.6

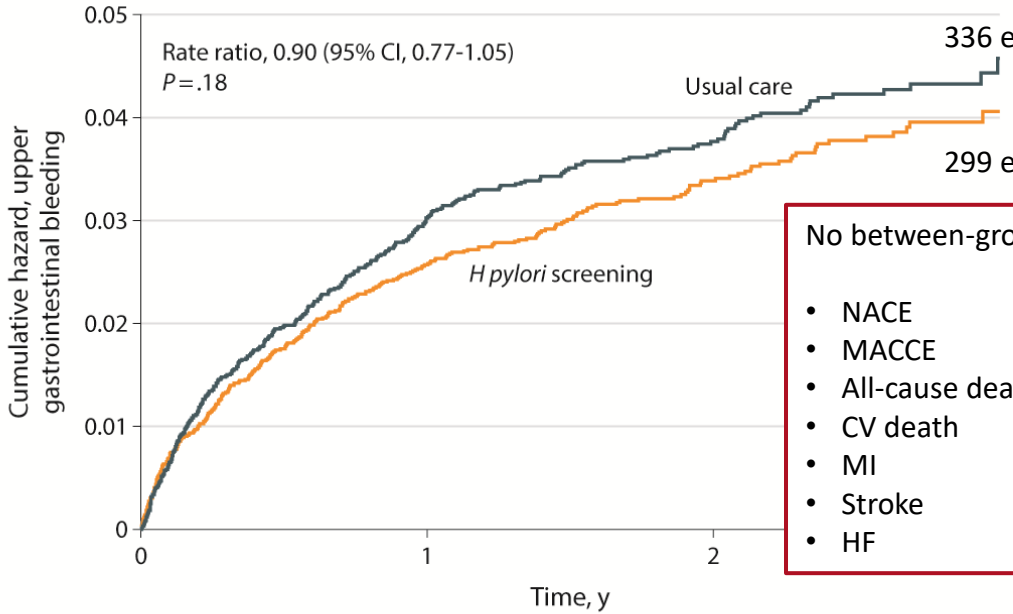
Eradication rate: 96.6

Characteristics of the Patients

Characteristic	No. (%) of patients	
	Helicobacter pylori screening (n = 9245)	Usual care (n = 9221)
Medication at discharge		
Statin	8725 (94.4)	8722 (94.6)
Aspirin	7817 (84.6)	7852 (85.2)
ACE inhibitor or ARB	7718 (83.5)	7632 (82.8)
β-Blocker	7002 (75.8)	6942 (75.3)
Proton pump inhibitor	5207 (56.3)	4550 (49.3)
Ticagrelor	4732 (51.2)	4927 (53.4)
Clopidogrel	2215 (24.0)	2280 (24.7)
Direct oral anticoagulation	1471 (15.9)	1514 (16.4)
Prasugrel	1108 (12.0)	743 (8.1)
Antithrombotic combination therapy, No. (%)		
Single antiplatelet therapy	1011 (10.9)	1013 (11.0)
Dual antiplatelet therapy	6522 (70.6)	6429 (69.7)
Oral anticoagulation with antiplatelet therapy	1498 (16.2)	1568 (17.0)

Primary end point

Upper Gastrointestinal Bleeding (UGIB)



336 events; cumulative hazard, 4.6%

299 events; cumulative hazard, 4.1%

No between-group differences with regard to:

- NACE
- MACCE
- All-cause death
- CV death
- MI
- Stroke
- HF

Secondary endpoints

Period	Events, No.	Total follow-up (per 1000 person-years)[a]	Incidence rate (per 1000 person-years)	Negative binominal Rate ratio (95% CI)[b]	P value crude[c]	P value adjusted[c]
Secondary end points						
Net adverse clinical event						
Usual care	1809	16.62	108.85	1.00 (0.93-1.07)	.97	.97
Screening	1818	16.92	107.42			
MACCE						
Usual care	1236	16.96	72.87	0.97 (0.89-1.05)	.41	.97
Screening	1213	17.27	70.22			
All-cause death						
Usual care	965	17.93	53.82	1.01 (0.92-1.10)	.88	.97
Screening	968	18.21	53.17			
Cardiovascular death						
Usual care	512	17.93	28.56	1.00 (0.88-1.13)	.97	.97
Screening	511	18.21	28.07			
Myocardial infarction						
Usual care	696	17.11	40.67	0.95 (0.85-1.06)	.38	.97
Screening	678	17.44	38.88			
Ischemic stroke						
Usual care	174	17.75	9.80	0.97 (0.78-1.21)	.80	.97
Screening	177	18.03	9.82			
Heart failure						
Usual care	490	17.43	28.11	0.97 (0.86-1.11)	.68	.97
Screening	485	17.69	27.42			

Sensitivity analyses

Similar results from sensitivity analyses using

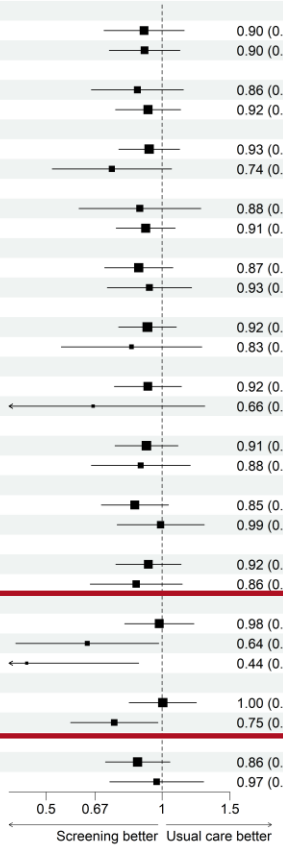
- Randomization inference
- Cox proportional hazard model
- Poisson model

- and predefined analyses using a modified follow-up (from admission, at 30 days, at 1 year, and 1–2-year follow-up, a landmark analysis starting 30 days after discharge)

corroborate robustness of the primary analysis.

UGIB in prespecified subgroups

Subgroup	H pylori screening N	H pylori screening N/100 years	Usual care N	Usual care N/100 years	Rate ratio (95% CI)
Age					
Below 75 years	131/5,563	1.16	146/5,514	1.34	0.90 (0.71, 1.14)
75 years or above	168/3,682	2.57	190/3,707	2.88	0.90 (0.73, 1.11)
Sex					
Female	97/2,636	1.96	114/2,692	2.29	0.86 (0.66, 1.13)
Male	202/6,609	1.57	222/6,529	1.77	0.92 (0.76, 1.12)
Current smoking					
No	233/7,260	1.66	250/7,188	1.83	0.93 (0.77, 1.11)
Yes	53/1,718	1.55	76/1,765	2.27	0.74 (0.52, 1.06)
Hypertension					
No	56/2,861	0.96	64/2,820	1.16	0.88 (0.61, 1.26)
Yes	243/6,384	2.03	272/6,401	2.27	0.91 (0.76, 1.08)
Diabetes					
No	177/6,773	1.33	207/6,805	1.57	0.87 (0.71, 1.07)
Yes	122/2,472	2.69	129/2,416	2.97	0.93 (0.72, 1.19)
Chronic kidney disease					
No	255/8,383	1.56	283/8,386	1.75	0.92 (0.77, 1.09)
Yes	41/714	3.67	51/742	4.37	0.83 (0.55, 1.27)
Previous alcohol use disorder					
No	190/5,912	1.78	219/5,955	1.83	0.92 (0.75, 1.12)
Yes	16/266	3.27	20/237	4.58	0.66 (0.34, 1.29)
Previous gastroduodenal pathology					
No	213/7,679	1.42	236/7,692	1.60	0.91 (0.75, 1.10)
Yes	86/1,566	3.00	100/1,529	3.66	0.88 (0.66, 1.18)
Previous MI					
No	182/6,121	1.52	216/6,209	1.82	0.85 (0.70, 1.04)
Yes	117/3,124	2.00	120/3,012	2.14	0.99 (0.76, 1.29)
Infarct type					
NSTEMI	200/5,750	1.83	219/5,667	2.03	0.92 (0.76, 1.12)
STEMI	96/3,347	1.47	115/3,461	1.75	0.86 (0.65, 1.13)
Anemia on admission					
No anemia	182/6,042	1.55	194/6,113	1.62	0.98 (0.80, 1.21)
Mild anemia	37/878	2.50	54/842	3.78	0.64 (0.42, 0.98)
Moderate to severe anemia	15/193	5.41	26/161	11.75	0.44 (0.23, 0.87)
Kidney failure on admission					
No	195/6,986	1.40	199/7,019	1.45	1.00 (0.82, 1.23)
Yes	104/2,222	2.72	135/2,181	3.60	0.75 (0.58, 0.97)
Proton pump inhibitor on admission					
No	200/6,961	1.46	231/6,946	1.74	0.86 (0.71, 1.05)
Yes	99/2,284	2.39	105/2,275	2.50	0.97 (0.73, 1.28)



Per-Protocol analysis

	H pylori screened patients		*H pylori* positive patients		Patients receiving eradication	
End point	Hazard ratio (95% CI)	P Value	Hazard ratio (95% CI)	P Value	Hazard ratio (95% CI)	P Value
UGIB	0.84 (0.65-1.08)	0.16	0.47 (0.22-1.01)	0.05	0.49 (0.23-1.06)	0.07

Lower point estimates but no significant difference in secondary outcomes.

Conclusions

In this nationwide cluster-randomized, crossover, registry-based clinical trial among unselected patients with acute MI, routine *H pylori* screening did not significantly reduce the risk of the primary end point of upper gastrointestinal bleeding.

However, a clinically relevant benefit of *H pylori* screening may exist at higher infection prevalence, lower PPI use and in subgroups at higher baseline risk of bleeding indicated by concomitant anemia or kidney failure may exist.

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Steering committee

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