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Reply to 'Screening for *Helicobacter pylori* infection in patients with cardiovascular and gastrointestinal disease'

We appreciate the interest by Jonatan Wärme and colleagues (Wärme, J. et al. Screening for *Helicobacter pylori* infection in patients with cardiovascular and gastrointestinal disease. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01028-8, 2024)[1] in our Review (Talasaz, A. H. et al. Optimizing antithrombotic therapy in patients with coexisting cardiovascular and gastrointestinal disease. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-01003-3, 2024)[2]. They propose that routine *H. pylori* screening and eradication might be a modifiable risk factor for gastrointestinal bleeding (GIB) in patients receiving antithrombotic agents. We find this hypothesis interesting and plausible but, for the reasons outlined below, we have reservations about consideration of *H. pylori* as an actionable treatment target to reduce the risk of bleeding in these patients.

Our reservations are largely related to the scarcity of high-quality data to show that the screening approach can both be used to identify individuals with a clinically important excess risk of bleeding in adjusted analyses of patients receiving antithrombotic agents (including anticoagulants) and is something to act on using proven tools that, when implemented, reduce the risk of bleeding. The assertion that *H. pylori* infection increases the risk of GIB is plausible but uncertain. One reference provided by Wärme et al. for this statement is for a retrospective cohort study in 1,719 patients with peptic ulcer bleeding and uncomplicated peptic ulcer disease diagnosed by endoscopy who were identified in the digital archive of a single hospital in Germany over a 10-year period[3]. *H. pylori*-positive status was associated with an increased risk of peptic ulcer bleeding in patients receiving aspirin (odds ratio 2.23) but not among those receiving anticoagulants[3]. The study, although interesting, has limitations with internal and external validity[3]. The other reference is a meta-analysis on the effect of *H. pylori* infection on the incidence of peptic ulcers in patients receiving low-dose aspirin[4]. Although the reported odds ratio for peptic ulcers in patients who were receiving low-dose aspirin and who were *H. pylori*-positive compared with those who were *H. pylori*-negative was 1.68 (95% CI 1.40–2.02)[4], the annual risk of bleeding from a peptic ulcer was reported in another meta-analysis to be only 1%[5], indicative of a low magnitude of risk.

Regarding therapies to mitigate the risk of bleeding associated with *H. pylori* infection, there is similar uncertainty. Two randomized clinical trials (RCTs) have focused on secondary prevention of recurrent ulcer bleeding[6,7]. One RCT involved 250 participants and reported no significant difference in (but a numerically higher incidence of) recurrent ulcer bleeding in the 6 months after *H. pylori* eradication compared with proton pump inhibitor (PPI) co-prescription (1.9% versus 0.9%)[6]. The other RCT did not focus specifically on the randomized treatment of *H. pylori* compared with no treatment[7]. Instead, PPI use was compared with placebo after treatment for *H. pylori* infection in 123 participants receiving low-dose aspirin who had previous ulcer complications[7]. Therefore, this trial does not directly inform the current conversation. The HEAT trial[8] was the only primary prevention RCT in patients receiving low-dose aspirin that aimed to mitigate the risk of upper GIB by routine eradication of *H. pylori* infection, but the trial had limitations. Patients randomly assigned to receive active eradication of *H. pylori* infection (involving treatment with antibiotics and a PPI) had significantly fewer bleeding events than patients in the placebo group during the 2.5 years of follow-up, but this significant difference was lost during longer-term follow-up[8]. Moreover, the observed effect might have been attributable to the PPI component of the treatment rather than to *H. pylori* eradication, but the trial did not have a PPI-only group to resolve this uncertainty. Also of note, one course of treatment does not eradicate *H. pylori* infection in approximately 20% of patients[9]. The evidence base for the potential effect of *H. pylori* infection on the risk of bleeding or how to mitigate it is even more scant for patients receiving anticoagulation.

Much like Wärme and colleagues, we await the completion of the ongoing HELP-MI trial (NCT05024864). We agree with Wärme et al. that *H. pylori* might be a plausible target, but we do not find sufficient evidence, at the moment, to recommend routine screening and eradication of *H. pylori* infection in patients receiving antithrombotic agents merely with the goal of reducing bleeding events.

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Competing interests
B.B. reports that he was a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of inferior vena cava (IVC) filters. B.B. has not been involved in the litigation in 2022–2024 nor has he received any compensation in 2022–2024. B.B. reports that he is a member of the Medical Advisory Board for the North American Thrombosis Forum and serves in the Data Safety and Monitory Board of the NAIL-IT trial funded by the National Heart, Lung, and Blood Institute, and Translational Sciences. B.B. is a collaborating consultant with the International Consulting Associates and the US Food and Drug Administration in a study to generate knowledge about utilization, predictors, retrieval and safety of IVC filters. Unrelated to this article, B.B. is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814). A.H.T. declares no competing interests.