Aspirin and *Helicobacter pylori* interaction

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The efficacy of aspirin in the prevention of cardiovascular disease needs to be balanced against the associated increased risk of bleeding, especially of gastrointestinal origin, which is the most common source. There is an urgent need to reduce bleeding events both in primary cardiovascular disease prevention, where the risk–benefit relationship is being questioned,[1] and in secondary cardiovascular disease prevention, where the benefits exceed the bleeding risk[2] but aspirin is often used in combination with other antiplatelet drugs, which increases the risk.

Several strategies have been proposed to minimise the risk of gastrointestinal bleeding in people taking aspirin, including aspirin dose reduction and long-term combination therapy with antisecretory drugs.[3] *Helicobacter pylori* is considered a risk factor for peptic ulcer bleeding in people taking aspirin.[4,5] A strategy to reduce this risk is to eradicate the infection in people taking aspirin, which is an attractive option because it is a short-term treatment with a long-term preventive effect, but the available studies have reported discordant results.[6,7,8] The Maastricht Consensus Conference[9] recommended that *H pylori* should be tested for and treated in patients on long-term aspirin treatment with high bleeding risk, who might need additional antisecretory therapy. However, the evidence to support this recommendation is limited.[9]

In *The Lancet*, Chris Hawkey and colleagues[10] report the results of the Helicobacter Eradication Aspirin Trial (HEAT), an awaited randomised, double-blind, placebo-controlled trial conducted in UK primary care, with the aim to provide a definitive answer to whether *H pylori* eradication is an effective strategy in the primary prevention of ulcer bleeding in people taking aspirin for cardiovascular disease prevention. 30 166 patients aged 60 years or older who had been prescribed aspirin at a dose of 325 mg or less per day and had urea breath testing for *H pylori*. 5353 patients had a positive breath-test result (mean age 73·6 years [SD 6·9], 3948 [72·8%] were male, and 1404 [26·2%] were female) and were randomly assigned to receive active *H pylori* eradication treatment or placebo for 7 days. Patients were followed up for a total of 26 668 person-years (median 5·0 years [IQR 3·9–6·4]). The primary outcome was time to hospitalisation or death due to definite or probable peptic ulcer bleeding. The Cox proportional hazards assumption was not met, and the primary outcome was subsequently analysed in two periods of 2·5 years each, which showed a significant reduction in incidence of the primary outcome in the active eradication group compared with the placebo group within the first 2·5 years (six episodes adjudicated as definite or probable peptic ulcer bleeds, rate 0·92 [95% CI 0·41–2·04] per 1000 person-years *vs* 17 episodes, rate 2·61 [1·62–4·19] per 1000 person-years; hazard ratio 0·35 [95% CI 0·14–0·89]; p=0·028), but not thereafter or in the overall period.

HEAT was a pragmatic trial that was difficult to conduct, and it did not meet the primary endpoint. Due to its event-driven design, recruitment and follow-up had to be prolonged for a median of 5 years, because the number of bleeding events was lower than expected. There were very few ulcer bleeds and the number of deaths due to bleeding events was extremely low compared with cardiovascular deaths. The trial results showed a progressive loss of aspirin-induced ulcer bleeding protection after *H pylori* eradication, and are difficult to interpret. However, the trial adds valuable information because the maximum follow-up of patients in the few small previously available clinical trials was only 12 months, and these trials were aimed at the secondary prevention of ulcer bleeding.[6,7,8]

The time-dependent loss of efficacy of the proposed strategy represents a missed opportunity for an interesting finding. The pragmatic nature of the study, allowing changes in aspirin, non-steroidal anti-inflammatory drugs, proton pump inhibitors, or antibiotic use over time, although accounted for in the statistical analysis, prevents firm conclusions from being made. Moreover, ascertainment of *H pylori* eradication was performed in only a small percentage of patients. The waning of the effect over time cannot be explained by time-related changes in the rate of bleeding events, which was higher in the first year of aspirin treatment than in subsequent years of treatment,[11] because the trial did not include patients who had not used aspirin previously (median duration of previous aspirin use was 2·3 years). This might have also led to selection of a population with low bleeding risk who were resistant to aspirin damage. In this regard, whether *H pylori* eradication might have greater efficacy in patients who have not used aspirin previously is an interesting hypothesis that was not addressed by the trial. Similarly, enrolment of a mix of patients taking aspirin for either

primary or secondary cardiovascular disease precluded the evaluation works the efficacy of *H pylori* eradication in patients taking aspirin who did not have cardiovascular disease, where the benefit–risk ratio is uncertain.[12]

HEAT is an important trial designed to evaluate the effect of *H pylori* eradication in patients taking aspirin for cardiovascular disease prevention, and the results showed that *H pylori* eradication confers some benefits in the primary prevention of ulcer bleeding in this population. However, the time-dependent loss of efficacy of this strategy, together with the very low rate of ulcer bleeding events, even in patients with confirmed infection, call into the question the need of a *H pylori* test-and-treat strategy for all patients taking aspirin for cardiovascular disease prevention. The effect of *H pylori* eradication was not as strong as expected, and should not change the current clinical practice guidelines,[9] which recommend *H pylori* eradication only in patients taking aspirin who are at high risk of bleeding. Furthermore, we still require studies designed to evaluate the effects of *H pylori* eradication in patients who have not used aspirin previously, for whom, based on findings of the HEAT trial, the benefits might be greater.

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The relationship between climate change, health, and the humanitarian response

The climate emergency is a humanitarian and health crisis. Extreme weather events, heat stress, declining air quality, changes in water quality and quantity, declining food security and safety, and changes in vector distribution and ecology threaten all of us.[1] As the planet heats, climate risks are increasingly complex, frequent, and unpredictable, compounding existing vulnerabilities and inequities within populations and causing emergencies that cascade across different systems and sectors.[2] Humanitarian agencies are now seeing how these problems are putting millions of people across the world at immediate risk of famine and death.[3]

An estimated 274 million people are now in need of humanitarian assistance—which has increased from 235 million in 2021.[4] As the 2022 *Lancet* Countdown on health and climate change[5] has identified, humanitarian needs will increase exponentially as poverty and food insecurity rise, the global supply chain and energy crises intensify, sociopolitical instability worsens, the collateral effects of COVID-19 become more apparent, and the intensity and frequency of climate-related events increase. These increasing needs occur within a shrinking humanitarian space characterised by underfunding and high rates of violence against humanitarian workers.[4]

Climate change is a threat multiplier, increasing the risk of climate-related crises, conflict, and displacement.[6] Climate change is also a major driver of food insecurity, which has been increasing globally for the last

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