to date have used the same dose and duration of vonoprazan. It is not known if better results could be achieved with longer durations of treatment. The only caution with these results is that more studies are required in countries outside of Japan. There is a higher frequency of poor metabolizers in Japanese populations (20%) compared with European populations (<6%). This group of poor metabolizers will have higher blood levels of standard PPI and consequently better acid suppression.[6] This will, if anything, decrease the difference between vonoprazan and standard PPI-based triple therapy in Japan.

Potent acid suppression with vonoprazan leads to better eradication rates but this effect can only partly retrieve the potency lost with antibiotic resistance to clarithromycin.[1] The rate of clarithromycin resistance is increasing worldwide—in Japan the resistance rate is 30%-35%.[2,7] Quadruple treatment has been recommended because of increasing antibiotic resistance but this treatment has a high frequency of adverse effects and poor compliance (particularly for a duration of 10-14 days).[8] Replacing PPIs with vonoprazan could bring the eradication rate for clarithromycin-based triple therapy into an acceptable range but this regimen will not be adequate for countries with higher rates of clarithromycin resistance. This trend towards increasing resistance to clarithromycin seems inevitable unless countries can adopt more stringent rules for antibiotic stewardship.[9]

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Editorial: replacing standard proton pump inhibitors with vonoprazan may breathe new life into triple therapy for *Helicobacter pylori*—authors' reply

We would like to thank Dr Fraser for his interest in our article.[1,2] As he indicated, the relatively low eradication rate of clarithromycin-resistant strains with standard triple therapy may be a concern, despite the replacement of proton pump inhibitors (PPIs) with vonoprazan. In addition, both PPI-based and vonoprazan-based standard triple therapies showed good eradication rates against clarithromycin-sensitive strains. These findings imply that vonoprazan-based triple therapy has an advantage only if prior susceptibility testing is unavailable in a clinical situation. Therefore, the role of vonoprazan should be further evaluated in alternative eradication regimens beyond the standard triple therapy, especially in regions where the clarithromycin resistance rate is high.

We recently published a network meta-analysis study on *Helicobacter pylori* eradication therapy in Korea,[3] where the clarithromycin

resistance rate is 21%–24%.[4] In that study, alternative regimens, including sequential, hybrid, and concomitant therapies, showed higher eradication rates than the standard triple therapy did. In addition, despite a relatively small number of comparisons, quinolone-based sequential therapy for 14 days demonstrated the best eradication rate among the 21 included regimens. Replacing PPIs with vonoprazan in those regimens (sequential, hybrid, concomitant, and quinolone-based sequential therapies) may show promising *H. pylori* eradication rates.

Of course, we believe that eradication therapy following antibiotic susceptibility testing is superior; however, vonoprazan-based therapy can be the second-best option, especially when susceptibility testing is not yet available in the country or hospital in question.

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Editorial: selective serotonin receptor inhibitors and gastrointestinal bleeding—managing the risk

Selective serotonin uptake inhibitors (SSRIs) have been associated with gastrointestinal bleeding in epidemiologic studies; this risk increases with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).

Two large systematic reviews have summarised the published data. Jiang et al. found a modest increase in the risk of GI bleeding in patients taking SSRIs; odds ratio (OR) 1.55 with 95% confidence interval (CI) 1.35-1.78.[1] Concomitant use of NSAIDs increased the risk but the concomitant use of proton pump inhibitors (PPIs) took it away. Anglin et al. also found an increased risk of GI bleeding in patients using SSRIs.[2] The risk of upper GI bleeding was further increased in patients using NSAIDs with SSRIs (OR: 4.25; 95% CI: 2.82-6.42). Both meta-analyses found significant heterogeneity among studies.

SSRIs might deplete serotonin from platelets and impair their aggregation. In support, there may be an increased risk of haemorrhagic stroke and post-partum haemorrhage in users of SSRIs.

Laursen et al. throw further light on this issue by demonstrating that SSRI use is not associated with adverse outcomes after GI bleeding.[3] Specifically, the re-bleeding rate after initial endoscopy was not affected by use of SSRIs. Although mortality was increased in SSRI users, the effect disappeared when adjusted for age, aspirin and NSAID use.

There are no prospective studies on SSRIs and GI bleeding and no evidence of a causal relationship. Both meta-analyses showed significant heterogeneity among studies; confounding factors not fully accounted for might explain the observed results.