Peptic ulcer disease

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The rapidly declining prevalence of *Helicobacter pylori* infection and widespread use of potent anti-secretory drugs means peptic ulcer disease has become substantially less prevalent than it was two decades ago. Management has, however, become more challenging than ever because of the threat of increasing antimicrobial resistance worldwide and widespread use of complex anti-thrombotic therapy in the ageing population. Peptic ulcers not associated with *H pylori* infection or the use of non-steroidal anti-inflammatory drugs are now also imposing substantial diagnostic and therapeutic challenges. This Seminar aims to provide a balanced overview of the latest advances in the pathogenetic mechanisms of peptic ulcers, guidelines on therapies targeting *H pylori* infection, approaches to treatment of peptic ulcer complications associated with anti-inflammatory analgesics and anti-thrombotic agents, and the unmet needs in terms of our knowledge and management of this increasingly challenging condition.

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Introduction

The term peptic ulcer refers to acid peptic injury of the digestive tract, resulting in mucosal break reaching the submucosa. Peptic ulcers are usually located in the stomach or proximal duodenum, but they can also be found in the oesophagus or Meckel's diverticulum. In this Seminar, the term peptic ulcer disease refers to peptic ulcers located in the stomach or duodenum.[1]

Traditionally, a hypersecretory acidic environment together with dietary factors or stress were thought to cause most peptic ulcer diseases, but the discovery of *Helicobacter pylori* infection and the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) in the second half of the 20th century have changed this perception.

Epidemiology

Lifetime prevalence of peptic ulcer disease in the general population has been estimated to be about 5–10%, and incidence 0·1–0·3% per year.[1–3] However, the prevalence and incidence of peptic ulcer disease is now probably lower than these estimates worldwide, especially in high-income countries, because epidemiological studies have shown a sharp decreasing trend in the incidence, rates of hospital admissions, and mortality associated with the disease in the past 20–30 years.[4–9] These decreasing numbers could be due to the introduction of new therapies, or they might be due to a cohort trend that cannot be fully explained by known causes (eg, *H pylori* infection and NSAID treatment). Many gastrointestinal diseases are characterised by rises and falls in prevalence,[4] suggesting that an underlying birth-cohort trend might be present for peptic ulcer disease. Mortality associated with peptic ulcer disease peaked in generations born at the end of the 19th century and fell in those born in the 20th century. Although the decrease noted includes all types of ulcers (*H pylori*-associated, NSAID-associated, and idiopathic), the overall pattern corresponds to the decreasing prevalence of *H pylori* infection in the population, in which a birth-cohort effect is also seen in countries with low prevalence of the infection. These observations emphasise the key role of *H pylori* infection in both the cause and documented temporal variations of peptic ulcer disease.[4–7]

In European countries with different health-care systems and socioeconomic status, between 1921 and 2004, the risk of dying from gastric ulcers preceded that of dying from duodenal ulcers by 10–30 years.[5] In Central America, South America, and Asia, a decline in mortality from gastric ulcers and duodenal ulcers has also been recorded, and showed a birth-cohort effect that was similar to that in Europe, with high rates reported in people born in the late 19th century and a 10–20-year delayed peak mortality for those with duodenal ulcers.[6] In Asia, a steady decline in the prevalence of peptic ulcer disease has been reported in different ethnic groups, including Malay, Chinese, and Indian populations, for the past 20 years. This decline paralleled a decrease in *H pylori*-associated peptic ulcer disease.[7]

Although increased use of NSAIDs or introduction of anti-secretory medications does not seem to explain trends in ulcer-related mortality reported by Sonnenberg,[5] other studies[8,9] have reported falling hospital admissions for complications of peptic ulcer disease in the 21st century, with an incidence of 79 cases per 100 000 people per year and less than 30 cases of peptic ulcer disease complications per 100 000 people per year.[8,9] The reduction in peptic ulcer disease complications might be associated with the widespread use of anti-secretory drugs around the world and a more rational use of NSAIDs than before[8–10] (appendix p 8).

Search strategy and selection criteria

We searched MEDLINE and Embase (from Jan 1, 2010, to March 31, 2016) using the terms "peptic ulcer" in combination with "clinical trials", "meta-analysis", "guideline", "epidemiology", "risk factors", "physiopathology", "genetics", or "diagnosis". We selected publications from the past 6 years, but did not exclude commonly cited references that we regarded as seminal work. Articles or reviews published in the past 15–20 years were also identified, and we selected those publications we judged relevant. We have also cited review articles and book chapters to provide readers with additional references and a more detailed overview than this Seminar.

See Online for appendix

Pathogenic mechanisms and risk factors

H pylori and the use of NSAIDs or aspirin are the main risk factors of both gastric and duodenal ulcers.[1,11–13] However, only a few people with *H pylori* infection or taking NSAIDs or aspirin develop peptic ulcer disease, suggesting that individual susceptibility to bacterial virulence and drug toxicity is essential to the initiation of mucosal damage.

The interaction between bacterial and host factors determines the outcome of *H pylori* infection. The ability of *H pylori* strains to produce different proteins has been linked to their virulence and to the host immune response.[1] The organism produces urease to create an alkaline environment, which is essential for its survival in the stomach under the mucosal barrier. It also expresses adhesins such as blood group antigen adhesin (BabA) or outer inflammatory protein adhesin (OipA), which facilitate attachment of bacteria to gastric epithelium. A genome pathogenic island encodes the virulent factors CagA and PicB, which—together with other bacterial factors—are thought to interact strongly with host tissue and be linked to gastric mucosal inflammatory cell infiltration and gastric epithelial injury (appendix p 9).[14–16] Almost all *H pylori* strains contain the *vacA* gene, which encodes a vacuolating cytotoxin, although half the strains do not express the protein. The role of VacA protein in disease pathogenesis is unclear.[16] Variations in the *vacA* gene structure (ie, a combination of signal sequence allelic types [s1a, 1b, and 2] and mid-region allelic types [m1 and m2]) might have functional implications. Most *cagA*-positive strains carry the *vacA*-s1 genotypes, whereas almost all *cagA*-negative strains are classified as *vacA* s2/m2 strains with low cytokine response and host interaction, which could have clinical consequences.[14–18]

Host interaction and the mucosal inflammatory response to *H pylori* can be determined, at least in part, genetically and define the outcome of peptic ulcer and other acid-related diseases.[14] Functional polymorphisms in different cytokine genes have been related to peptic ulcer disease. Interleukin 1β, encoded by *IL1B*, is a cytokine associated with the inflammatory response to *H pylori* infection and with inhibition of gastric secretion.[19] Polymorphisms of *IL1B* affect mucosal interleukin 1β production in diverse populations, suggesting that these polymorphisms have a role in the pathogenesis of *H pylori*-associated gastroduodenal diseases, including peptic ulcer disease.[14,20–24] Genes encoding tumour necrosis factor and lymphotoxin-α have also proved to be associated with duodenal ulcers, gastric ulcers, and antral inflammation caused by *H pylori* infection.[25–27] A genome-wide association study and meta-analysis[28] identified an association between the locus of Toll-like receptor 1 (*TLR1*) and *H pylori* seroprevalence in a white population with European ancestry. Other cytokines have also been linked to the pathogenesis of *H pylori*-induced diseases, but their role is unclear.[14]

NSAIDs and aspirin are the other major risk factors linked to peptic ulcer disease and its complications. Compared with non-users, NSAID and aspirin use increase the risk of complications of peptic ulcer disease by four times in NSAID users, and by two times in aspirin users.[13,29,30] As well as NSAID and aspirin use or *H pylori* infection, complications are largely driven by comorbidity[31] and ageing.[32–34] Concomitant use of NSAIDs or aspirin with selective serotonin-reuptake inhibitors, corticosteroids, aldosterone antagonists, or anticoagulants substantially increase the risk of upper gastrointestinal bleeding.[33] The role of smoking and poor socioeconomic status is unclear.[34] Studies have shown a link between aspirin use and an increased risk of peptic ulcer disease in patients carrying some specific genetic polymorphisms, but the clinical relevance of these studies also remains to be determined.[35–39]

Many people who habitually take NSAIDs or aspirin have concurrent *H pylori* infection. The interaction of these two factors in peptic ulcer disease is controversial. Randomised controlled trials have shown that eradication of *H pylori* is beneficial in patients who start taking NSAIDs but not in those who are on long-term NSAID treatment.[40] A meta-analysis[13] of observational studies found that uncomplicated peptic ulcer disease was more common in *H pylori*-positive patients than in *H pylori*-negative patients (odds ratio [OR] 2·12, 95% CI 1·68–2·67). The interpretation of this meta-analysis was that both *H pylori* infection and the use of NSAIDs and aspirin independently increase the risk of peptic ulcer disease, and that the disease was uncommon in patients without *H pylori* infection who do not take NSAIDs or aspirin.[13,41,42]

H pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease can be diagnosed in at least a fifth of cases.[43] Life-threatening conditions could also induce the disease. For example, soon after the Great East Japan Earthquake in 2011, an unusual increase in cases of *H pylori*-negative haemorrhagic multiple peptic ulcer disease was recorded.[44] Accommodation in a refugee shelter was a strong risk factor for peptic ulcer bleeding after a large-scale disaster.[45] A Danish study[46] showed that psychological stress was associated with an increased incidence, in part by influencing health risk behaviours, and had similar effects on the disease related or unrelated to either *H pylori* or NSAIDs. The true prevalence of idiopathic peptic ulcer disease not related to NSAIDs or *H pylori* infection is unknown because a molecular investigation of patients with chronic gastritis but negative for *H pylori* showed that almost half were false negatives.[47]

Pathophysiology

How *H pylori* induces the development of different types of lesions in the gastroduodenal mucosa is not completely understood. Inflammation associated with *H pylori* infection can result in either hypochlorhydria or hyperchlorhydria,[48] and thus determine the type of peptic ulcer formed. These effects can be mediated by cytokines

that inhibit parietal cell secretion,[49] or directly by *H pylori* products on the H^+/K^+ ATPase α-subunit, activation of calcitonin-gene related peptide (CGRP) sensory neurons linked to somatostatin, or inhibition of gastrin.[50] Pangastritis is associated with hyposecretion and linked to the formation of gastric ulcers. However, 10–15% of patients with *H pylori* infection have antral predominant gastritis associated with duodenal ulcers and increased gastric secretion derived from hypergastrinaemia and reduced antral somatostatin content.[51] Inhibition of somatostatin and the subsequent stimulation of gastrin increases histamine secretion from enterochromaffin-like cells, leading to increased secretion of acid or pepsin from parietal and gastric chief cells. The importance of the interaction between somatostatin and gastrin in this process seems clear, because the number of D-cells and somatostatin levels are reduced, whereas G:D cell ratios and gastrin:somatostatin ratios are increased, in the antral tissue of patients with duodenal ulcers. Conversely, eradication of *H pylori* is followed by an increase in somatostatin mRNA expression and a concomitant decrease in gastrin mRNA expression in patients with duodenal ulcers.[52] Gastric hypersecretion in antral-predominant gastritis and inadequate feedback inhibition might be associated with an acidic environment and the development of gastric metaplasia in the duodenal bulb, which might be colonised by and favour ulcer formation in the bulb[15] (appendix p 10).

NSAIDs damage the gastroduodenal mucosa through both systemic and local mechanisms, but the systemic inhibition of constitutively expressed cyclooxygenase 1 (COX-1)-derived prostaglandins is regarded as the main mechanism. Reduced mucosal prostaglandin values are associated with low mucus and bicarbonate secretion, inhibition of cell proliferation, and decreased mucosal blood flow, which are essential to maintenance of mucosal integrity. The COX hypothesis is supported by studies showing that coadministration of exogenous prostaglandins reduces mucosal damage.[53] COX-2-selective NSAIDs, which spare COX-1, reduce the risk of ulcers.[54] However, this hypothesis does not fully explain the spectrum of mucosal damage. People taking NSAIDs could have a profound decrease in mucosal prostaglandins without necessarily developing gastric lesions.[55–58] NSAIDs have different physicochemical properties and a wide range of pK_a values, which account for some differences in their toxicity and extent of topical damage.[55]

NSAIDs initiate mucosal damage in the cell through disruption of mucus phospholipids or the cell membrane and by uncoupling of mitochondrial oxidative phosphorylation. The loss of mucosal integrity is followed by tissue reaction amplified by luminal content such as acid, pepsin, food, bile, and *H pylori*.[57–59] Therefore, COX-derived prostaglandin inhibition, vascular damage, and topical effects are the main players in the pathogenesis of ulcers caused by NSAIDs (appendix p 11).

Low-dose aspirin can also induce mucosal damage in patients through both topical and systemic mechanisms, although direct evidence of the systemic effect is weak.[60,61] Once the damage has been induced, prostaglandins derived from both constitutively expressed COX-1 and inducible COX-2 enzymes seem to have a central role in mucosal repair, since non-selective and COX-2-selective NSAIDs have been shown to delay healing of peptic ulcers.[57,62]

The pathogenic mechanisms behind the development of idiopathic peptic ulcers are largely unknown. An imbalance between mucosal defensive mechanisms and aggressive factors, including a gastric acid hypersecretory status, is believed to exist. However, most gastric secretion studies were done in the pre-*H pylori* era, and we now know that most of the alterations were secondary to the effect of *H pylori* infection. Other possible pathogenetic factors include ischaemia, drugs, metabolic disturbances, viruses, histamine, radiotherapy, basophilia, and eosinophilic infiltration.[63]

Clinical presentation and diagnosis

Symptoms of peptic ulcer disease have limited predictive value because they are non-specific. Patients with duodenal ulcers typically feel hungry or have nocturnal abdominal pain. By contrast, patients with gastric ulcers have postprandial abdominal pain, nausea, vomiting, and weight loss. Patients with untreated peptic ulcer disease typically have relapsing symptoms because of spontaneous healing and relapse while the causal factor (eg, *H pylori* infection or NSAID use) persists. Elderly patients with peptic ulcer disease are frequently asymptomatic or have only mild symptoms.

Bleeding, perforation, or gastric outlet obstruction are the main complications of peptic ulcer disease. Bleeding, which manifests as melena or haematemesis, can occur without any warning symptoms in almost half of patients.[64] Hospital admissions for peptic ulcer bleeding have declined steadily worldwide, but the case fatality rate remains stable at 5–10%.[8,9] Perforation typically presents with sudden onset of intense pain in the upper abdomen. Dependent on age and comorbidity, mortality can be as high as 20%.

Endoscopy is the gold standard for diagnosis of peptic ulcer disease. Apart from exclusion of malignant disease, detection of *H pylori* infection with histology or rapid urease tests is essential to the subsequent treatment plan. Since *H pylori* is the cause of most types of peptic ulcer disease, a test-and-treat strategy with a non-invasive test (eg, urea breath and stool antigen tests) to exclude infection has been advocated in patients younger than 50–55 years (dependent on geographical areas) who present with non-investigated dyspepsia and no alarming symptoms in geographical regions where gastric cancer is uncommon and the prevalence of *H pylori* infection is greater than 20%.[65] In older patients, upper gastrointestinal endoscopy is the recommended test to exclude or confirm the disease.

	Drug combinations	Regimen	Recommended duration
Triple therapy	PPI plus amoxicillin* plus clarithromycin	Double dose† of PPI every 12 h 1000 mg amoxicillin every 12 h 500 mg clarithromycin every 12 h	14 days
Quadruple non-bismuth-based concomitant therapy	PPI plus amoxicillin plus clarithromycin plus metronidazole	Standard dose of PPI every 12 h 1000 mg amoxicillin every 12 h 500 mg clarithromycin every 12 h 500 mg metronidazole every 12 h	14 days
Bismuth-based quadruple therapy	PPI plus bismuth subcitrate plus tetracycline plus metronidazole	Standard dose of PPI every 12 h 120 mg bismuth subcitrate every 6 h 500 mg tetracycline every 6 h 500 mg metronidazole every 8 h	14 days
Fluoroquinolone-based triple therapy‡	PPI plus amoxicillin plus levofloxacin with or without bismuth	Standard dose of PPI every 12 h 1000 mg amoxicillin every 12 h 500 mg levofloxacin every 24 h 240 mg bismuth every 12 h	14 days
Rifabutin-based triple therapy§	PPI plus amoxicillin plus rifabutin	Standard dose of PPI every 12 h 1000 mg amoxicillin every 12 h 150 mg rifabutin every 12 h	10 days

Other regimens used in the treatment of *Helicobacter pylori* combine different antibiotics with similar results (eg, triple therapy could combine a proton pump inhibitor [PPI] plus amoxicillin plus metronidazole or PPI plus metronidazole plus clarithromycin). Sequential quadruple therapy consists of a 5-day dual therapy with a PPI and amoxicillin followed by a 5-day triple therapy with a PPI plus clarithromycin plus tinidazole or metronidazole. Hybrid quadruple therapies combine 10–14 days of dual therapy with PPI and amoxicillin with 7 days of treatment with clarithromycin and metronidazole at the end (or start, for reverse therapy). *Use metronidazole if patients have penicillin allergy. †Double doses: omeprazole 40 mg, lansoprazole 60 mg, rabeprazole 40 mg, esomeprazole 40 mg. ‡Used as rescue regimen; bismuth-based therapy can be added to these drugs (for fluoroquinolone-based quadruple therapy). §To be used when at least three recommended options have failed and if *H pylori* susceptibility testing is not available.

Table 1: **Most frequent regimens recommended for treatment of *Helicobacter pylori* infection in peptic ulcer disease**[67,68]

Management

Prevention of ulcer recurrence is the most important long-term goal to reduce morbidity and mortality. The appendix (p 12) provides an overview of the management of peptic ulcer disease. Mounting evidence suggests that eradication of *H pylori* infection alone is sufficient to heal associated peptic ulcers and to prevent relapse and recurrent bleeding in the absence of maintenance acid suppressive therapy. However, successful treatment of *H pylori* infection is a global challenge because of the growing prevalence of antibiotic resistance. The standard first-line therapies used to be regimens, consisting of a proton-pump inhibitor (PPI) and two antibiotics, such as clarithromycin plus amoxicillin or metronidazole given for 7–14 days (termed PPI-based triple therapy).[35,66–68] With increasing prevalence of antibiotic resistance, however, the effectiveness of *H pylori* eradication with this regimen has fallen from more than 90% two decades ago to less than 70% now in many countries.[67,68] Ideally, treatment should be based on antimicrobial susceptibility tests. Since these tests are not widely available, the choice of first-line therapies should be based on local prevalence of antibiotic resistance.[67–69] If susceptibility testing is not feasible, PPI-based triple therapy regimens containing clarithromycin should be abandoned in areas where the local clarithromycin resistance rate is more than 15%.[67–69]

In areas with low resistance to clarithromycin or when individual susceptibility to clarithromycin has been confirmed, PPI-clarithromycin-amoxicillin or PPI-clarithromycin-metronidazole regimens can be used. The rate of eradication can be increased with the use of high-dose PPI (twice the conventional dose) and by extending the duration of triple therapy from 7 days to a maximum of 14 days.[40,68–73] The recommended standard first-line therapy is either a bismuth-containing quadruple therapy for 14 days (PPI, a bismuth salt, tetracycline, and metronidazole) or a non-bismuth-based quadruple concomitant therapy (PPI, clarithromycin, amoxicillin, and metronidazole) for 14 days; both regimens have an eradication rate of more than 90% (table 1).[67,68,70,74,75]

Sequential therapy is another form of quadruple therapy, which consists of a 5-day dual therapy with a PPI and amoxicillin followed by a 5-day triple therapy with a PPI, clarithromycin, and tinidazole or metronidazole. Overall, the eradication rate of sequential therapy is better than that of 7-day and 10-day triple therapy regimens but not better than the eradication rate of 14-day triple therapy, bismuth-based therapy, and non-bismuth-based concomitant therapy,[76,77] and this treatment is not recommended (figure 1).[40,67,68] Hybrid quadruple therapies combine 10–14 days of dual therapy with PPI and amoxicillin with 7 days of treatment with clarithromycin and metronidazole. Hybrid quadruple therapy has shown similar effectiveness to quadruple concomitant or sequential quadruple therapy, and is more effective in non-Italian populations than in other populations studied.[78,79] In a Japanese cohort,[80] vonoprazan, a potent, novel, potassium-competitive acid blocker, combined with amoxicillin and clarithromycin or metronidazole as a first-line or second-line treatment, achieved an eradication rate of more than 90% in patients with a history of peptic ulcer disease.

For rescue therapy, levofloxacin-containing triple therapy (PPI, levofloxacin, and amoxicillin) achieves eradication rates of 74–81% as a second-line therapy in areas with low (<10%) quinolone resistance.[40,67,68,81] However, a rapid increase in primary quinolone resistance to *H pylori* reduces the effectiveness of levofloxacin-containing therapy.[81–83] A bismuth-containing quadruple therapy is an effective second-line therapy after failure of standard triple therapies, with eradication rates of 77–93%. This regimen is recommended after failure of other non-bismuth-containing quadruple therapies.[67,68] The addition of bismuth to a levofloxacin-containing triple regimen means that a triple-therapy regimen becomes a quadruple-therapy regimen.[68,84] All these strategies are now recommended to be used for 14 days.[67,68] Susceptibility testing is strongly recommended after one treatment is unsuccessful (if an endoscopy is done and a non-bismuth-based therapy is considered) or after two consecutive treatment failures.[68] When culture of *H pylori* is not available, or when at least three recommended options have been unsuccessful, rifabutin-based triple therapy

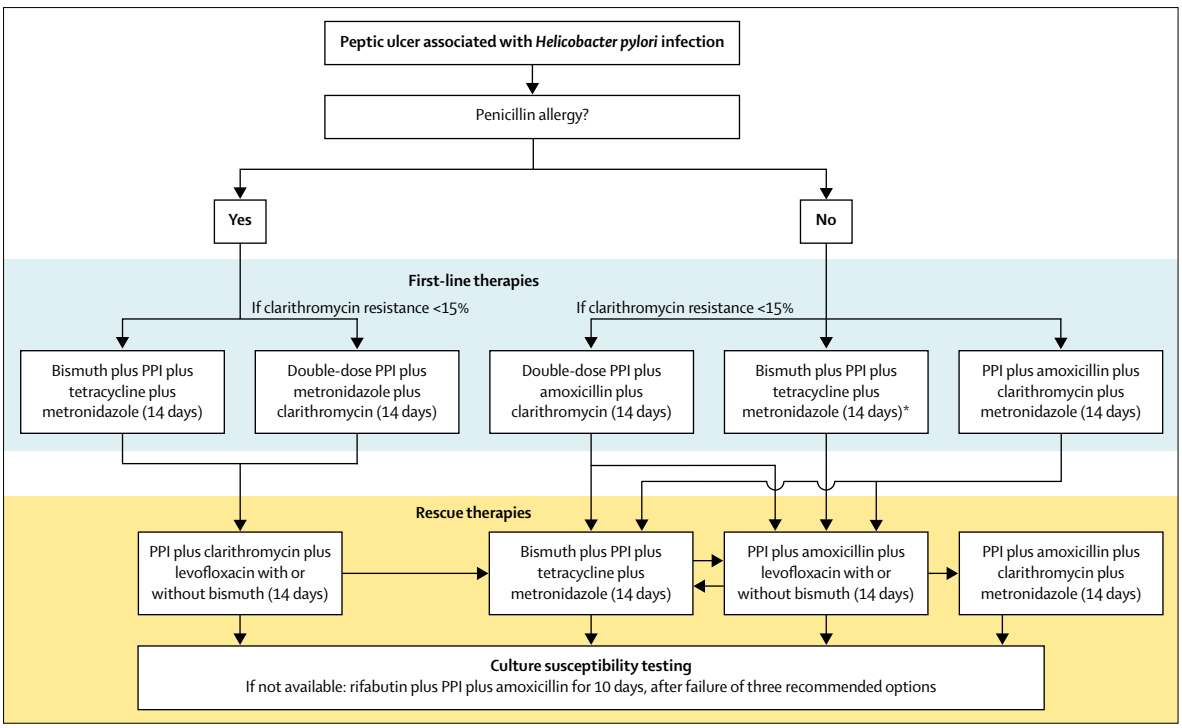

***Figure 1*: Algorithm for management of *Helicobacter pylori* in peptic ulcer disease**
PPI=proton pump inhibitor. *Preferred option in areas with high resistance to clarithromycin and metronidazole.

(PPI, rifabutin, and amoxicillin) for 10 days is an effective rescue option, with eradication rates of 66–70%.[85,86] In patients with penicillin allergy, a bismuth-based quadruple therapy is recommended as first-line treatment, and a fluoroquinolone-based regimen can be used as a rescue option. In areas of low (<15%) clarithromycin resistance, a PPI-clarithromycin-metronidazole combination could be prescribed as a first-line treatment (figure 1; table 1).[67,68]

There is growing interest in the use of probiotics as an adjuvant therapy to increase *H pylori* eradication rates and reduce antibiotic-related adverse events, although further studies are needed.[67,68] A randomised phase 3 trial[87] of an oral recombinant *H pylori* vaccine recruited more than 4400 children in China who had no current or past *H pylori* infection. The investigators reported a vaccine efficacy of 71·8% in 3 years.[87]

NSAIDs and aspirin are the most important cause of peptic ulcer disease in high-income countries where the prevalence of *H pylori* is declining.[1] Since *H pylori*-associated ulcers cannot be differentiated from NSAID-associated ulcers, testing and treating of *H pylori* is recommended. More than 85% of NSAID-associated or aspirin-associated ulcers heal with 6–8 weeks of PPI therapy, provided that NSAIDs or aspirin are discontinued. Ulcer healing can be achieved, but it is delayed if patients continue to use NSAIDs.

Co-therapy with an antisecretory agent is a recommended preventive strategy for patients at risk of NSAID-associated or aspirin-associated peptic ulcer disease. In a randomised placebo-controlled trial,[88] a histamine H_2 receptor antagonist was effective in prevention of ulcers in average-risk aspirin users. Whether PPI is better than an H_2 receptor antagonist for aspirin users has yielded conflicting results. One randomised trial[89] found that famotidine was inferior to pantoprazole for prevention of upper gastrointestinal bleeding or severe dyspepsia. By contrast, a multicentre randomised trial[90] found that, among high-risk aspirin users, rates of recurrent bleeding were similar between the groups receiving PPI and standard-dose H_2 receptor antagonist. PPIs are clearly effective for the prevention of ulcer bleeding with aspirin. However, famotidine might be a reasonable alternative for patients who do not comply with or want to be on PPIs in the long term.

The role of *H pylori* infection in aspirin users with ulcer bleeding deserves further investigation. In a 7-year prospective cohort study[91] of aspirin users presenting with ulcer bleeding, one cohort of *H pylori*-positive patients resumed aspirin without gastroprotective therapy after eradication of *H pylori* was confirmed. The cumulative incidence of recurrent ulcer bleeding in these patients did not differ substantially from that of average-risk aspirin users with no history of ulcers.[91] This finding suggests that eradication of *H pylori* is associated with a low risk of recurrent ulcer bleeding with aspirin use even in the absence of gastroprotective therapy.

Among NSAID users, many strategies are available for the prevention of gastroduodenal ulcers and their

	Low gastrointestinal risk*	High gastrointestinal risk†
Low cardiovascular risk	Non-selective NSAIDs	Non-selective NSAIDs plus PPI; celecoxib plus PPI‡; eradicate *Helicobacter pylori*§
High cardiovascular risk¶	Naproxen; add PPI if patient is taking aspirin	No NSAIDs; naproxen plus PPI; low-dose celecoxib plus aspirin plus PPI might be an alternative option

Prevention of peptic ulcer disease and associated complications in patients on non-steroidal anti-inflammatory drug (NSAID) treatment requires assessment of the presence of both gastrointestinal and cardiovascular risk factors.[92–94] PPI=proton pump inhibitor. *No risk factors. †Presence of risk factors (patients aged 60 years or older, with a history of ulcers, or patients on concomitant medication with antiplatelet agents, anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors). ‡Especially indicated in patients with a complicated ulcer history or the presence of several risk factors. §In patients with a history of ulcers, adopt a test-and-treat strategy with the use of non-invasive tests (urea breath and stool antigen tests) to exclude *H pylori* infection, although invasive tests with endoscopy are also possible. ¶Use risk charts (eg, Framingham risk scores or the European SCORE system) to estimate cardiovascular risk on the basis of several variables. Patients with a history of cardiovascular events or diabetes are considered at high cardiovascular risk. In most cases, aspirin co-therapy might be indicated. Cyclooxygenase 2 (COX-2)-selctive NSAIDs are contraindicated by the European Medicines Agency (EMA) in patients with a history of cardiovascular events.

***Table 2*: Management of peptic ulcer disease prevention in patients on NSAIDs**

complications. These strategies include co-therapy of NSAIDs with a PPI, H_2 receptor antagonist, or misoprostol; substitution of non-selective NSAIDs with COX-2-selective NSAIDs; or combination of a COX-2-selective NSAID with a gastroprotective agent.[92–94] PPIs are the most popular prophylactic agents. A systematic review and meta-analysis[95] consisting of more than 125 000 participants found that combination of COX-2-selective NSAIDs and a PPI offers the best protection against peptic ulcer complications. This combination was followed in effectiveness by COX-2-selective NSAIDs alone, non-selective NSAIDs plus a PPI, and non-selective NSAIDs plus misoprostol.[95] Unlike low-dose aspirin, no evidence exists that H_2 receptor antagonists can prevent ulcer bleeding associated with NSAIDs. Another meta-analysis[96] found that standard doses of H_2 receptor antagonists cannot reduce the risk of gastric ulcers. Although misoprostol effectively prevents peptic ulcer complications with NSAIDs, gastrointestinal upset and abortifacient actions limit the use of misoprostol for gastric protection. The gastroprotective effect of PPIs seems a class effect[97] and is not dose-dependent.

Patients taking NSAIDs often use aspirin, non-aspirin antiplatelet drugs, anticoagulants, and corticosteroids. Although concomitant aspirin use reduces the gastrointestinal-sparing effect of COX-2 inhibitors,[92,96] indirect evidence suggests that patients taking COX-2 inhibitors and aspirin might have fewer peptic ulcer complications than do those taking non-selective NSAIDs and aspirin. In a meta-analysis[96] of 17 276 patients, the risk of clinically significant outcomes was lower in the group receiving aspirin plus a COX-2-selective NSAID than in the group receiving aspirin plus a non-selective NSAID (relative risk 0·72, 95% CI 0·62–0·95). A similar conclusion has been reached in another meta-analysis.[98] These data, however, were derived from a post-hoc analysis.[96,98] Table 2 summarises the management of peptic ulcer disease prevention with NSAIDs, which requires assessment of both gastrointestinal and cardiovascular risk factors, since NSAIDs might also increase the risk of major cardiovascular events.[54,92–94]

Notably, NSAIDs and aspirin can cause lower gastrointestinal bleeding and acid suppression cannot prevent mucosal damage beyond the duodenum. Two large-scale randomised trials[99,100] that used a combined endpoint of upper and lower gastrointestinal events showed that celecoxib was more effective than a non-selective NSAID plus a PPI. The advantage of celecoxib over non-selective NSAIDs plus a PPI is attributable to a substantial reduction in anaemia secondary to presumed small bowel bleeding. However, different non-selective NSAIDs vary in their tendency to cause lower gastrointestinal bleeding, and data suggest that PPIs could aggravate NSAID-induced small bowel injury through dysbiosis.[101] Whether the superiority of celecoxib in the lower gastrointestinal tract recorded in these two large-scale trials can be extrapolated to other non-selective NSAIDs remains unclear.

Most cases of peptic ulcer disease heal after 6–8 weeks of PPI therapy. If ulcers fail to heal, drug compliance should be checked. Blood tests and a carefully taken patient history can often reveal continuous or surreptitious use of NSAIDs, which is often overlooked in patients with refractory ulcers.[102] Doubling of PPI dose for another 6–8 weeks is often recommended, although no reliable evidence proves that this strategy is better than standard-dose PPI in this setting. Serological tests could be useful to detect false-negative *H pylori* infection. After exclusion of surreptitious use of NSAIDs or aspirin, or false-negative *H pylori* status, unusual causes of peptic ulcer should be explored, examples of which include malignancies, infections (eg, cytomegalovirus), Crohn's disease, vasculitis, upper abdominal radiotherapy, crack cocaine use, and Zollinger-Ellison syndrome, which is associated with high acid secretion and often causes the development of multiple ulcers extending to the distal duodenum.

With the declining prevalence of *H pylori* infection, patients with idiopathic ulcers are increasingly being recognised, and these patients could be at increased risk of recurrence, bleeding complications, and death.[103,104] Although long-term PPI therapy is often recommended, no evidence is available that this approach will improve clinical outcomes.[105]

Management of peptic ulcer bleeding

Bleeding peptic ulcers account for 40–60% of all causes of acute upper gastrointestinal bleeding.[8] Timely endoscopic treatment and acid suppressive therapy are key for successful outcomes. Although surgery is the cornerstone for management of patients with uncontrolled or massive recurrent bleeding, radiological intervention has also gained importance in recent years.

Patients presenting with upper gastrointestinal bleeding should be assessed promptly and resuscitation should begin with crystalloid solutions. Transfusion policy should be restrictive and aimed to maintain haemoglobin concentrations over 70 g/L, as this approach

has been associated with reduced mortality.[106] Risk stratification should identify high-risk patients for early intervention and reduce the duration of hospital stay for low-risk patients. The Rockall and Glasgow-Blatchford scores have been extensively studied. A Glasgow-Blatchford score of zero accurately identifies patients not requiring treatment in hospital.[107]

Maintenance of a neutral gastric pH seems essential to prevent platelet disaggregation and clot lysis over the eroded artery of a bleeding peptic ulcer. Peak acid suppression after intravenous administration of a PPI occurs within hours, compared with several days later after oral administration. The intravenous route of administration offers a faster onset of gastric suppression, achievement of intragastric pH closer to neutrality, and better bioavailability than the oral route.[108] A meta-analysis[109] of randomised controlled trials showed that pre-emptive intravenous high-dose PPIs led to a decreased proportion of patients with high-risk endoscopic stigmata and reduced the need for endoscopic haemostatic treatment, but intravenous administration of PPIs should not substitute or delay early endoscopy for high-risk patients. Tranexamic acid and antifibrinolytic agents do not seem to be effective in this setting.[110] Prokinetic agents, such as intravenous erythromycin and metoclopramide, given before endoscopy have improved endoscopic view and reduce the need for a second look endoscopy[111] (panel).

Early endoscopy done within 24 h provides prognostic information based on endoscopic stigmata and effective therapy. In a meta-analysis[112] of randomised controlled trials, endoscopic treatment was shown to reduce rebleeding, surgery, and mortality. Endoscopy also identifies low-risk patients suitable for early hospital discharge. Endoscopic treatment is indicated in ulcers showing active bleeding, a non-bleeding visible vessel, or an adherent clot. Two meta-analyses[113,114] of randomised controlled trials have shown that addition of a second modality to epinephrine injection is better than epinephrine injection alone in reducing recurrent bleeding, surgery, and mortality.

Acid suppression has a crucial role in prevention of recurrent bleeding after initial endoscopic haemostasis. In a systematic review of 24 trials,[110] PPI therapy reduced recurrent bleeding and need for surgery. A substantial reduction in mortality was also noted in a subgroup of patients with active bleeding or non-bleeding visible vessels. The optimum dose of a PPI after endoscopy continues to be controversial. A meta-analysis[115] of randomised controlled trials found that high-dose PPIs and low-dose PPIs were similarly effective in reducing the risk of recurrent ulcer bleeding. High-dose PPIs were defined as a dose equivalent to an 80 mg bolus of omeprazole or pantoprazole, followed by continuous intravenous infusion of the drug at 8 mg/h for 72 h. Continuous-infusion doses exceeding 192 mg per day were also considered high-dose PPIs. Other doses were considered low-dose PPIs. However, this meta-analysis included trials with suboptimum design, such as ulcers with low-risk endoscopic stigmata. Another meta-analysis,[116] which was largely based on trials done in Asia, found that intermittent high-dose PPI therapy was not less effective than continuous infusion of a PPI in patients with

Panel: **Strategies for management of bleeding peptic ulcers**

Before endoscopy

Risk stratification

Glasgow-Blatchford scores are superior to Rockall scores in prediction of endoscopic treatment and surgery. A Glasgow-Blatchford score of zero reliably predicts early discharge without intervention.

Restrictive blood transfusion strategy

Blood transfusion when haemoglobin values are below 70 g/L leads to less rebleeding and better survival than does liberal transfusion.

Correction of anticoagulation with a target INR of about 1·5

The optimum INR remains undefined, and recommendations are based on expert opinion only.

Use of prokinetic drugs

Prokinetic drugs lead to improved endoscopic view, and reduce the need for second look endoscopy.

Pre-emptive PPIs

Pre-emptive PPIs reduce the presence of high-risk stigmata at endoscopy, and reduce the need for endoscopic therapy.

Endoscopic treatment

Addition of a second modality to epinephrine injection reduces recurrent bleeding and need for surgery.

Endoscopy within 24 h

There is no clear evidence that immediate endoscopy offers advantages over endoscopy done within 24 h.

Combination therapy

PPIs reduce rebleeding and the need for surgery.

After endoscopy

Mantain or initiate (if not started before endoscopy) PPI therapy.

Adjuvant PPI therapy

Treatment with high-dose parenteral PPI indicated if high-risk peptic ulcer stigmata present. Oral PPI given if patients had no high-risk peptic ulcer stigmata.

High-dose PPI infusion for 72 h

Intermittent high-dose PPI therapy seems similar to continuous high-dose PPI infusion.

Recurrent bleeding

Further endoscopic treatment versus early surgery

One randomised controlled trial showed a higher rate of complications in the group that underwent surgery than in the group that received repeat endoscopy. High mortality was recorded in both groups. Shock and an ulcer size with a diameter greater than 2 cm was predictive of endoscopic treatment failure.

Angiographic embolisation

Retrospective studies suggested a higher rebleeding rate in the angiography group than in the surgery group, but no difference in mortality.

INR=international normalised ratio. PPI=proton pump inhibitor.

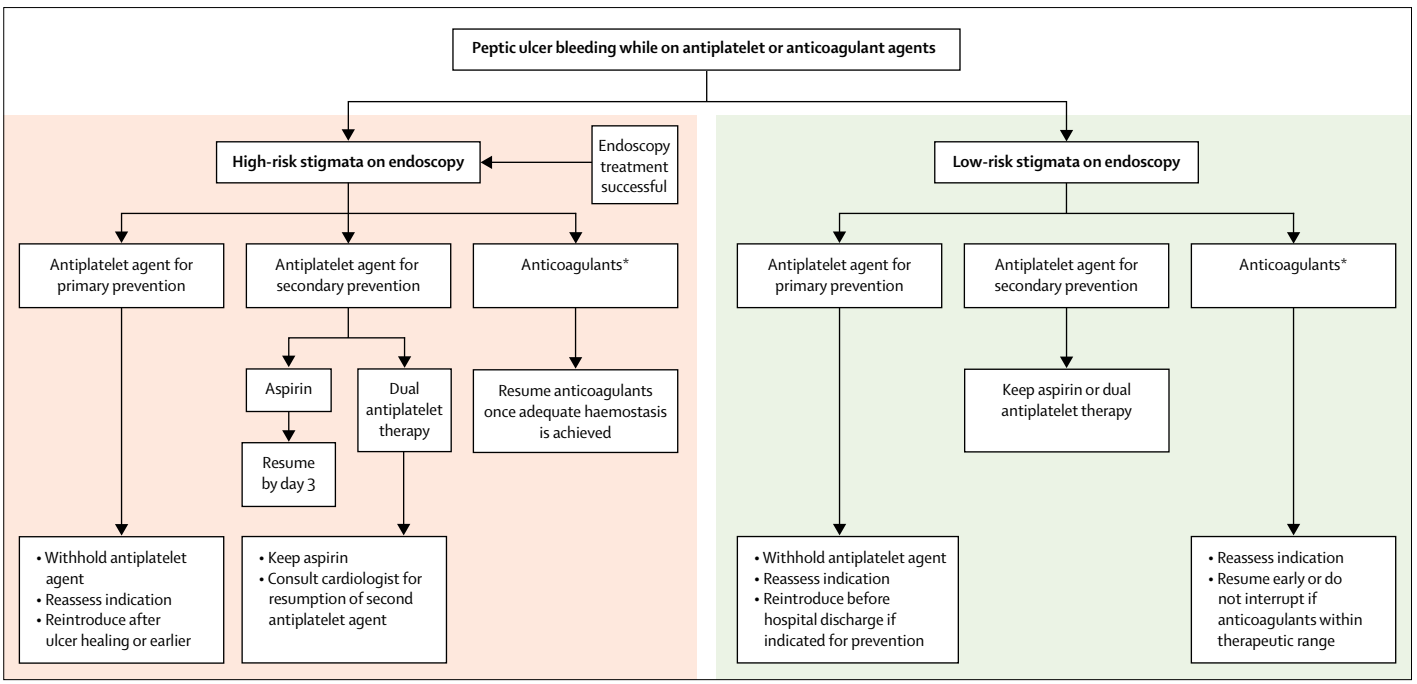

***Figure 2*: Management of antiplatelet or anticoagulant therapy in patients who develop peptic ulcer bleeding**
Modified from Gralnek and colleagues,[123] by permission of Thieme Medical Publishers. In patients at high risk of developing cardiovascular disease, early resumption of antiplatelet or anticoagulant therapy is recommended, because although the risk of rebleeding increases, overall mortality decreases. *Vitamin K or prothrombin complex concentrates should be considered in patients with bleeding associated with warfarin overdose.

high-risk stigmata. Unlike Asian populations, most North American and European populations carry genetic polymorphisms associated with rapid metabolism of PPIs.[117] Therefore, whether intermittent high-dose PPI is as effective as continuous high-dose PPI infusion in all high-income populations remains uncertain. Continuous high-dose PPI infusion is still the preferred post-endoscopic adjuvant treatment for high-risk patients (panel).

Uncontrolled or recurrent bleeding is the most important adverse prognostic factor predicting mortality. In a randomised study[118] comparing endoscopic retreatment with surgery after an initial endoscopy, large ulcers and hypotension were predictive of failure to repeat endoscopic treatment. Early surgery or angiographic embolisation are potential alternative options for these high-risk patients[110,118] (panel).

Management of patients on antiplatelet or anti-thrombotic therapy complicated by upper gastrointestinal bleeding is difficult because the data are scanty. Decisions often need to be tailored to individual patients on the basis of the severity of bleeding and risk of thromboembolism. In aspirin users with peptic ulcers complicated by bleeding and requiring endoscopic treatment, a randomised controlled trial showed that those who continued to take aspirin had a two-times increased risk of recurrent bleeding but a ten-times reduced risk of all-cause mortality at 8 weeks compared with those who discontinued aspirin.[119] Patients receiving dual antiplatelet therapy for a drug-eluting stent should avoid stopping both antiplatelet drugs even for a brief period, because of the high risk of stent thrombosis.[120,121]

Patients receiving warfarin complicated by severe gastrointestinal bleeding resulting from coagulopathy can be treated with vitamin K, fresh frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa. Fresh frozen plasma could precipitate fluid overload. High-dose vitamin K should be avoided because it will extend the time required for re-warfarinisation, thereby increasing the risk of thromboembolism. Prothrombin complex concentrates are preferred in patients with severe bleeding. Recombinant factor VIIa should be reserved for uncontrolled life-threatening bleeding because it increases the risk of thrombosis. The use of direct oral anticoagulants (DOACs) has gained popularity. A meta-analysis[122] of randomised trials showed that DOACs are more effective than warfarin in reducing thromboembolic risk. However, some DOACs have been associated with a higher risk of major gastrointestinal bleeding than warfarin.[122] Unlike bleeding induced by warfarin, that induced by DOACs cannot be reversed by vitamin K. Activated charcoal given within 4 h of ingestion can be used to treat toxicity resulting from DOAC overdose. The value of prothrombin complex concentrate or recombinant factor VIIa for massive bleeding associated with DOACs remains uncertain. Haemodialysis can be used for life-threatening bleeding with dabigatran but not for other DOACs. Idarucizumab has been approved by the

For more on **idarucizumab** see http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm467396.htm

US Food and Drug Administration (FDA) for reversal of uncontrolled bleeding in patients receiving dabigatran.

The optimum timing for resuming anticoagulant therapy is largely based on retrospective data or expert opinion.[123,124] Warfarin should be resumed once adequate haemostasis has been achieved. For patients with high thromboembolic risk, such as those with a metallic mitral valve replacement, low-molecular-weight heparin should be given on the same day of resuming warfarin until a satisfactory international normalised ratio is achieved. With the rapid onset of action of DOACs and the absence of effective or approved agents for most oral anticoagulants, re-initiation of these drugs should be delayed until adequate haemostasis has been achieved. Figure 2 summarises the standard position on the optimum timing of resuming antiplatelet or anticoagulant therapy after a peptic ulcer disease bleeding event (appendix pp 1–4).

Controversies and future research questions

The global decline of peptic ulcer disease during the past century has occurred most rapidly in the past two decades. This decreasing trend could be related to a cohort effect that occurred before the introduction of potent anti-secretory agents and *H pylori* treatment.[4–9] The parallel decline in the prevalence of *H pylori* infection resulting from improvements in socioeconomic status has had an important role. Widespread use of PPIs has probably also contributed to the rapid decline of peptic ulcer disease. However, an overuse of PPIs, which are estimated to be used inappropriately in almost 50% of cases, might have led to unexpected new side-effects that are now being gradually unravelled.[10] The reduction of *H pylori*-associated, NSAID-associated, and aspirin-associated peptic ulcer disease has uncovered idiopathic disease. The occurrence of idiopathic ulcers seems to be increasing and is associated with high mortality.[103,104] The mechanisms and optimum management of idiopathic disease will need to be defined.

How *H pylori* infection and NSAID or aspirin interact remains controversial, and the best strategy to manage patients with both risk factors to prevent the onset of peptic ulcer disease is a contested and unresolved issue. The ongoing HEAT trial[125] in the UK to investigate whether *H pylori* eradication will reduce the incidence of hospital admissions for ulcer bleeding in aspirin users might provide some answers.

The pathogenesis of a wide range of *H pylori*-related gastric lesions is still not fully understood. Development of these lesions is probably led by a combination of *H pylori* virulent factors and the host immune response, but the specific combination of *H pylori* factors and the host genetic profile has not yet been clarified. Technological advances in genome-wide association studies might provide some insight by identifying genetic polymorphisms associated with peptic ulcer disease in specific populations. Why some patients are more susceptible than others to the gastric toxicity of NSAIDs and aspirin also remains unclear.

Antibiotic resistance continues to be a major challenge for successful treatment of *H pylori* infection. New therapies are in fact old therapies with different drug combinations and longer durations of treatment. Molecular targets against essential bacterial proteins could be key to resolving antibiotic resistance.[126]

Complications of peptic ulcer disease, such as bleeding, remain life-threatening. Advances in endoscopic and pharmacological therapies have not substantially reduced the mortality associated with such bleeding, because comorbidities are now the major cause of death in these patients. Increasing use of anti-thrombotic agents in patients with multiple comorbidities has led to new challenges in the management of bleeding. Prospective data and randomised controlled trials are urgently needed to define the best strategy for patient care (appendix pp 1–5).

Contributors

AL and FKLC contributed equally in the literature search, in designing the structure of the manuscript, and in writing the manuscript.

Declaration of interests

AL has served as a consultant to Bayer Pharma AG and his institution has received a researcher-initiated grant on aspirin chemoprevention from Bayer Pharma AG. FKLC has served as a consultant to Pfizer, Eisai, Takeda, and Otsuka. FLKC has received an independent research grant from Pfizer and has been paid lecture fees (including for his service on speakers' bureaus) by Pfizer, AstraZeneca, and Takeda.

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References

1 Del Valle J. Peptic ulcer disease and related disorders. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine (19th edn). New York, NY: McGraw Hill Education, 2015: 1911–32.

2 Rosenstock SJ, Jørgensen T. Prevalence and incidence of peptic ulcer disease in a Danish County—a prospective cohort study. *Gut* 1995; **36:** 819–24.

3 Kurata JH, Nogawa AN, Abbey DE, Petersen F. A prospective study of risk for peptic ulcer disease in seventh-day adventists. *Gastroenterology* 1992; **102:** 902–09.

4 Sonnenberg A. Review article: historic changes of *Helicobacter pylori*-associated diseases. *Aliment Pharmacol Ther* 2013; **38:** 329–42.

5 Sonnenberg A. Time trends of ulcer mortality in Europe. *Gastroenterology* 2007; **132:** 2320–27.

6 Sonnenberg A. Time trends of ulcer mortality in non-European countries. *Am J Gastroenterol* 2007; **102:** 1101–07.

7 Leow AH, Lim YY, Liew WC, Goh KL. Time trends in upper gastrointestinal diseases and *Helicobacter pylori* infection in a multiracial Asian population — a 20-year experience over three time periods. *Aliment Pharmacol Ther* 2016; **43:** 831–37.

8 Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. The changing face of hospitalisation due to gastrointestinal bleeding and perforation. *Aliment Pharmacol Ther* 2011; **33:** 585–91.

9 Malmi H, Kautiainen H, Virta LJ, Färkkilä N, Koskenpato J, Färkkilä MA. Incidence and complications of peptic ulcer disease requiring hospitalisation have markedly decreased in Finland. *Aliment Pharmacol Ther* 2014; **39:** 496–506.

10 Lanas A. We are using too many PPIs, and we need to stop: a European perspective. *Am J Gastroenterol* 2016; **111:** 1085–86.

11 Zhang BB, Li Y, Liu XQ, Wang PJ,Yang B, Bian DL. Association between vacA genotypes and the risk of duodenal ulcer: a meta-analysis. *Mol Biol Rep* 2014; **41:** 7241–54.

12 Sugimoto M, Yamaoka Y. The association of vacA genotype and *Helicobacter pylori*-related disease in Latin American and African populations. *Clin Microbiol Infect* 2009; **15:** 835–42.

13 Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; **359:** 14–22.

14 Datta D, Roychoidhury S. To be or not to be: the host genetic factor and beyond *Helicobacter pylori* mediated gastro-duodenal diseases. *World J Gastroenterol* 2015; **21:** 2883–95.

15 Shiotani A, Graham DY. Pathogenesis and therapy of gastric and duodenal ulcer disease. *Med Clin North Am* 2002; **86:** 1447–66.

16 Yamaoka Y, Graham DY. *Helicobacter pylori* virulence and cancer pathogenesis. *Future Oncol* 2014; **10:** 1487–500.

17 Wang F, Meng W, Wang B, Qiao L. *Helicobacter pylori*-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345:** 196–20.

18 Chen MY, He CY, Meng X, Yuan Y. Association of *Helicobacter pylori* babA2 with peptic ulcer disease and gastric cancer. *World J Gastroenterol* 2013; **19:** 4242–51.

19 Guo T, Qian JM, Zhao YQ, Li XB, Zhang JZ. Effects of IL-1β on the proliferation and apoptosis of gastric epithelial cells and acid secretion from isolated rabbit parietal cells. *Mol Med Rep* 2013; **7:** 299–305.

20 Furuta T, El-Omar EM, Xiao F, Shirai N, Takashima M, Sugimura H. Interleukin 1β polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. *Gastroenterology* 2002; **123:** 92–105.

21 El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; **404:** 398–402.

22 Chakravorty M, Ghosh A, Choudhury A, Santra A, Hembrum J, Roychoudhury S. Interaction between IL1B gene promoter polymorphisms in determining susceptibility to *Helicobacter pylori* associated duodenal ulcer. *Hum Mutat* 2006; **27:** 411–19.

23 García-González MA, Lanas A, Savelkoul PH, et al. Association of interleukin 1 gene family polymorphisms with duodenal ulcer disease. *Clin Exp Immunol* 2003; **134:** 525–31.

24 Robert A, Olafsson AS, Lancaster C, Zhang WR. Interleukin-1 is cytoprotective, antisecretory, stimulates PGE2 synthesis by the stomach, and retards gastric emptying. *Life Sci* 1991; **48:** 123–34.

25 Zhang BB, Liu XZ, Sun J, Yin YW, Sun QQ. Association between TNF α gene polymorphisms and the risk of duodenal ulcer: a meta-analysis. *PLoS One* 2013; **8:** e57167.

26 Trejo-de la OA, Torres J, Sánchez-Zauco N, et al. Polymorphisms in TLR9 but not in TLR5 increase the risk for duodenal ulcer and alter cytokine expression in the gastric mucosa. *Innate Immun* 2015; **21:** 706–13.

27 Lanas A, García-González MA, Santolaria S, et al. TNF and LTA gene polymorphisms reveal different risk in gastric and duodenal ulcer patients. *Genes Immun* 2001; **2:** 415–21.

28 Mayerle J, den Hoed CM, Schurmann C, et al. Identification of genetic loci associated with *Helicobacter pylori* serologic status. *JAMA* 2013; **309:** 1912–20.

29 Lanas A, García-Rodríguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006; **55:** 1731–38.

30 Lanas Á, Carrera-Lasfuentes P, Arguedas Y, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015; **13:** 906–12.

31 Crooks CJ, West J, Card TR. Comorbidities affect risk of nonvariceal upper gastrointestinal bleeding. *Gastroenterology* 2013; **144:** 1384–93.

32 Chan FK, Goto S, Wu MS, et al. Burden of nonsteroidal anti-inflammatory and antiplatelet drug use in Asia: a multidisciplinary working party report. *Clin Gastroenterol Hepatol* 2012; **10:** 753–60.

33 Masclee GM, Valkhoff VE, Coloma PM, et al. Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology* 2014; **147:** 784–92.

34 González-Pérez A, Sáez ME, Johansson S, Nagy P, García Rodríguez LA. Risk factors associated with uncomplicated peptic ulcer and changes in medication use after diagnosis. *PLoS One* 2014; **9:** e101768.

35 Tanikawa C, Urabe Y, Matsuo K, et al. A genome-wide association study identifies two susceptibility loci for duodenal ulcer in the Japanese population. *Nat Genet* 2012; **44:** 430–34.

36 García-González MA, Bujanda L, Quintero E, et al. Association of PSCA rs2294008 gene variants with poor prognosis and increased susceptibility to gastric cancer and decreased risk of duodenal ulcer disease. *Int J Cancer* 2015; **137:** 1362–73.

37 Shiotani A, Murao T, Fujita Y, et al. Single nucleotide polymorphism markers for low-dose aspirin-associated peptic ulcer and ulcer bleeding. *J Gastroenterol Hepatol* 2014; **29** (suppl 4)**:** 47–52.

38 Wang PY, Chen HP, Chen A, et al. Impact of blood type, functional polymorphism (T-1676C) of the COX-1 gene promoter and clinical factors on the development of peptic ulcer during cardiovascular prophylaxis with low-dose aspirin. *Biomed Res Int* 2014; **2014:** 616018.

39 Shiotani A, Fujita Y, Nishio K. Low-dose aspirin-associated upper and mid gastrointestinal tract damage and gene polymorphism. *Curr Pharm Des* 2015; **21:** 5066–72.

40 Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61:** 646–64.

41 Sostres C, Carrera-Lasfuentes P, Benito R, et al. Peptic ulcer bleeding risk. The role of *Helicobacter pylori* infection in NSAID/low-dose aspirin users. *Am J Gastroenterol* 2015; **110:** 684–89.

42 Gisbert JP, Calvet X. Review article: *Helicobacter pylori*-negative duodenal ulcer disease. *Aliment Pharmacol Ther* 2009; **30:** 791–815.

43 Charpignon C, Lesgourgues B, Pariente A, et al. Peptic ulcer disease: one in five is related to neither *Helicobacter pylori* nor aspirin/NSAID intake. *Aliment Pharmacol Ther* 2013; **38:** 946–54.

44 Yamanaka K, Miyatani H, Yoshida Y, et al. Hemorrhagic gastric and duodenal ulcers after the Great East Japan earthquake disaster. *World J Gastroenterol* 2013; **19:** 7426–32.

45 Kanno T, Iijima K, Koike T, et al. Accommodation in a refugee shelter as a risk factor for peptic ulcer bleeding after the Great East Japan Earthquake: a case-control study of 329 patients. *J Gastroenterol* 2015; **50:** 31–40.

46 Levenstein S, Rosenstock S, Jacobsen RK, Jorgensen T. Psychological stress increases risk for peptic ulcer, regardless of *Helicobacter pylori* infection or use of nonsteroidal anti-inflammatory drugs. *Clin Gastroenterol Hepatol* 2015; **13:** 498–506.

47 Kiss S, Zsikla V, Frank A, Willi N, Cathomas G. *Helicobacter*-negative gastritis: polymerase chain reaction for *Helicobacter* DNA is a valuable tool to elucidate the diagnosis. *Aliment Pharmacol Ther* 2016; **43:** 924–32.

48 Meyer-Rosberg K, Scott DR, Rex D, Melchers K, Sachs G. The effect of environmental pH on the proton motive force of *Helicobacter pylori*. *Gastroenterology* 1996; **111:** 886–900.

49 Beales IL, Calam J. Inhibition of carbachol stimulated acid secretion by interleukin 1β in rabbit parietal cells requires protein kinase C. *Gut* 2001; **48:** 782–89.

50 Zaki M, Coudron PE, McCuen RW, Harrington L, Chu S, Schubert ML. *H. pylori* acutely inhibits gastric secretion by activating CGRP sensory neurons coupled to stimulation of somatostatin and inhibition of histamine secretion. *Am J Physiol Gastrointest Liver Physiol* 2013; **304:** G715–22.

51 El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997; **113:** 15–24.

52 Moss SF, Legon S, Bishop AE, Polak JM, Calam J. Effect of *Helicobacter pylori* on gastric somatostatin in duodenal ulcer disease. *Lancet* 1992; **340:** 930–32.

53 Silverstein FE, Graham GY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatoy drugs. *Ann Int Med* 1995; **123:** 241–49.

54 Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; **382:** 769–79.

55 Bjarnason I, Scarpignato C, Takeuchi K, Rainsford KD. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment Pharmacol Ther* 2007; **26:** 95–106.

56 Ligumski M, Golanska EM, Hansen DG, Kauffman GL. Aspirin can inhibit gastric mucosal cyclo-oxigenase without causing lesions in the rat. *Gastroenterology* 1983; **84:** 756–61.

57 Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology* 1997; **112:** 1000–16.

58 Lanas A, Panés J, Piqué JM. Clinical implications of COX-1 and/or COX-2 inhibition for the distal gastrointestinal tract. *Curr Pharm Des* 2003; **9:** 2253–66.

59 Sigthorsson G, Tibble J, Hayllar J, et al. Intestinal permeability and inflammation in patients on NSAIDs. *Gut* 1998; **43:** 506–51.

60 Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; **117:** 17–25.

61 Sostres C, Lanas A. Gastrointestinal effects of aspirin. *Nat Rev Gastroenterol Hepatol* 2011; **8:** 385–94.

62 Perini RF, Ma L, Wallace JL. Mucosal repair and COX-2 inhibition. *Curr Pharm Des* 2003; **9:** 2207–11.

63 McColl KE. *Helicobacter pylori*-negative nonsteroidal anti-inflammatory drug-negative ulcer. *Gastroenterol Clin North Am* 2009; **38:** 353–61.

64 Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol Suppl* 1999; **56:** 18–24.

65 Agréus L, Talley NJ, Jones M. Value of the "Test & Treat" strategy for uninvestigated dyspepsia at low prevalence rates of *Helicobacter pylori* in the population. *Helicobacter* 2016; **23:** 186–91.

66 Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific consensus guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2009; **24:** 1587–600.

67 Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016; **151:** 51–69.

68 Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut* 2017; **66:** 6–30.

69 Graham DY, Laine L. The Toronto *Helicobacter pylori* consensus in context. *Gastroenterology* 2016; **151:** 9–12c.

70 Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. *Gut* 2016; **65:** 870–78.

71 Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. *Gastroenterology* 2013; **145:** 121–28.

72 Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database Syst Rev* 2013; **12:** CD008337.

73 Villoria A, Garcia P, Calvet X, Gisbert JP, Vergara M. Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2008; **28:** 868–77.

74 Sun Q, Liang X, Zheng Q, et al. High efficacy of 14-day triple therapy-based, bismuth-containing quadruple therapy for initial *Helicobacter pylori* eradication. *Helicobacter* 2010; **15:** 233–38.

75 Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of *Helicobater pylori*. *Aliment Pharmacol Ther* 2011; **34:** 604–17.

76 Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013; **347:** f4587.

77 Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication. *Cochrane Database Syst Rev* 2016; **6:** CD009034.

78 Hsu PI, Lin PC, Graham DY. Hybrid therapy for *Helicobacter pylori* infection: a systemic review and meta-analysis. *World J Gastroenterol* 2015; **21:** 12954–62.

79 Hsu PI, Kao SS, Wu DC, et al. A randomized controlled study comparing reverse hybrid therapy and standard triple therapy for *Helicobacter pylori* infection. *Medicine* 2015; **94:** e2104.

80 Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. *Gut* 2016; **65:** 1439–46.

81 Chen PY, Wu MS, Chen CY, et al. Systematic review with meta-analysis: the efficacy of levofloxacin triple therapy as the first- or second-line treatments of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2016; **44:** 427–37.

82 Trespalacios-Rangél AA, Otero W, Arévalo-Galvis A, Poutou-Piñales RA, Rimbara E, Graham DY. Surveillance of levofloxacin resistance in *Helicobacter pylori* isolates in Bogotá-Colombia (2009–2014). *PLoS One* 2016; **11:** e0160007.

83 Chuah SK, Liang CM, Lee CH, et al. A randomized control trial comparing 2 levofloxacin-containing second-line therapies for *Helicobacter pylori* eradication. *Medicine* 2016; **95:** e3586.

84 Gisbert JP, Romano M, Gravina AG, et al. *Helicobacter pylori* second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. *Aliment Pharmacol Ther* 2015; **41:** 768–75.

85 Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylor*i infection. *Aliment Pharmacol Ther* 2012; **35:** 209–21.

86 Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12:** 177–86.

87 Zeng M, Mao XH, Li JX, et al. Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **386:** 1457–64.

88 Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 119–25.

89 Ng FH, Wong SY, Lam KF, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology* 2010; **138:** 82–88.

90 Chan FK, Kyaw M, Tanigawa T, et al. Similar efficacy of proton-pump inhibitors vs H2-receptor antagonists in reducing risk of upper gastrointestinal bleeding or ulcers in high-risk users of low-dose aspirin. *Gastroenterology* 2017; **152:** 105–10.e1.

91 Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013; **144:** 528–35.

92 Scarpignato C, Lanas A, Blandizzi C, Lems WF, Hermann M, Hunt RH, for the International NSAID Consensus Group. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Med* 2015; **13:** 55.

93 Scheiman JM, Fendrick AM. Summing the risk of NSAID therapy. *Lancet* 2007; **369:** 1580–81.

94 Chan FK. Primer: managing NSAID-induced ulcer complications—balancing gastrointestinal and cardiovascular risks. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3:** 563–73.

95 Yuan JQ, Tsoi KK, Yang M, et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. *Aliment Pharmacol Ther* 2016; **43:** 1262–75.

96 Rostom A, Muir K, Dube C, Lanas A, Jolicoeur E, Tugwell P. Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug Health Patient Saf* 2009; **1:** 47–71.

97 Regula J, Butruk E, Dekkers CP, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole. *Am J Gastroenterol* 2006; **101:** 1747–55.

98 Yuan JQ, Yang M, Threapleton DE, et al. Systematic review with meta-analysis: the gastrointestinal benefits of COX-2 selective inhibitors with concomitant use of low-dose aspirin. *Aliment Pharmacol Ther* 2016; **44:** 785–95.

99 Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* 2010; **376:** 173–79.

100 Cryer B, Li C, Simon LS, Singh G, Stillman MJ, Berger MF. GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial. *Am J Gastroenterol* 2013; **108:** 392–400.

101 Wallace JL, Syer S, Denou E, et al. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury by inducing dysbiosis. *Gastroenterology* 2011; **141:** 1314–22.

102 Lanas AI, Remacha B, Esteva F, Sáinz R. Risk factors associated with refractory peptic ulcers. *Gastroenterology* 1995; **109:** 1124–33.

103 Hung LC, Ching JY, Sung JJ, et al. Long-term outcome of *Helicobacter pylori*-negative idiopathic bleeding ulcers: a prospective cohort study. *Gastroenterology* 2005; **128:** 1845–50.

104 Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with *Helicobacter pylori*-negative idiopathic bleeding ulcers. *Gastroenterology* 2009; **137:** 525–31.

105 Wong GL, Au KW, Lo AO, et al. Gastroprotective therapy does not improve outcomes of patients with *Helicobacter pylori*-negative idiopathic bleeding ulcers. *Clin Gastroenterol Hepatol* 2012; **10:** 1124–29.

106 Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368:** 11–21.

107 Stanley AJ, Dalton HR, Blatchford O, et al. Multicenter comparison of the Glasgow Blatchford and Rockall Scores in the prediction of clinical end-points after upper gastrointestinal hemorrhage. *Aliment Pharmacol Ther* 2011; **34:** 470–75.

108 Baker DE. Peptic ulcer bleeding following therapeutic endoscopy: a new indication for intravenous esomeprazole. *Rev Gastroenterol Disord* 2009; **9:** E111–18.

109 Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; **7:** CD005415.

110 Lau JY, Barkun A, Fan DM, Kuipers EJ, Yang YS, Chan FK. Challenges in the management of acute peptic ulcer bleeding. *Lancet* 2013; **381:** 2033–43.

111 Barkun A, Bardou M, Martel M, Gralnek IM, Sung JY. Prokinetics in acute upper GI bleeding: a meta-analysis. *Gastrointest Endosc* 2010; **72:** 1138–45.

112 Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992; **102:** 139–48.

113 Sung JJ, Tsoi KK, Lai LH, Wu JC, Lau JY. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. *Gut* 2007; **56:** 1364–73.

114 Marmo R, Rotondano G, Bianco MA, Piscopo R, Prisco A, Cipolletta L. Outcome of endoscopic treatment for peptic ulcer bleeding: is a second look necessary? A meta-analysis. *Gastrointest Endosc* 2003; **57:** 62–67.

115 Wang CH, Ma MH, Chou HC, et al. High-dose vs. non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2010; **170:** 751–58.

116 Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA Intern Med* 2014; **174:** 1755–62.

117 Hunfeld N, Touw D, Mathot R, Mulder P, Van Schaik R, Kuipers E. A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism. *Aliment Pharmacol Ther* 2010; **31:** 150–59.

118 Lau JY, Sung JJ, Lam YH, et al. Endoscopic re-treatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med* 1999; **340:** 751–56.

119 Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010; **152:** 1–9.

120 Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007; **116:** 745–54.

121 Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug eluting stent implantation. *JAMA* 2007; **297:** 159–68.

122 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383:** 955–62.

123 Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012; **17:** 1–8.

124 Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47:** a1–46.

125 Dumbleton JS, Avery AJ, Coupland C, et al. The Helicobacter Eradication Aspirin Trial (HEAT): a large simple randomised controlled trial using novel methodology in primary care. *EBioMedicine* 2015; **2:** 1200–04.

126 Cremades N, Velázquez-Campoy A, Martínez-Júlvez M, et al. Discovery of specific flavodoxin inhibitors as potential therapeutic agents against *Helicobacter pylori* infection. *ACS Chem Biol* 2009; **4:** 928–38.