Annals of Medicine and Surgery 82 (2022) 104760

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Review

Efficacy, safety and cost-effectiveness of vonoprazan vs Proton Pump Inhibitors in reflux disorders and H. pylori eradication: A literature review

Muhammad Shehryar [a], Rana Uzair Ahmad [a], Hira Khalid Kareem [a], Laiba Khan [b], Muhammad Fawad Ashraf [a], Ahtizaz Hassan [b], Sabeena Saeed [b], Haseeb Khan Tareen [a,*], Dr Adnan Nazir [c], Muhammad Aizaz Ashraf [d]

[a] Mayo Hospital, Anarkali, Lahore, 54000, Punjab, Pakistan
[b] HIT Hospital, Taxila Cantt, Rawalpindi, Punjab, Pakistan
[c] Aurora St. Lukes' Medical Center, Milwaukee, WI, USA
[d] Nishtar Medical University, Medical Unit 2, Multan, Punjab, Pakistan

A B S T R A C T

Gastroesophageal reflux disease (GERD) is one of the most prevalent conditions worldwide and is conventionally treated by proton pump inhibitor therapy. However, around 40% of people have reported some form of resistance to this therapy. Vonoprazan has recently been approved for the treatment of GERD. Literature was searched on PubMed, Google Scholar, Embase and Medline. Inclusion criteria were 1) Human subjects; 2) papers published in English language; 3) study types that are RCTs.

In pre-clinical studies, VPZ was unaffected by changes in pH, making it 1.2–2 times more potent than PPI, both in-vivo and in-vitro. In studies involving GERD, several RCTs proved higher efficacy of VPZ than conventional PPI. RCTs on patients affected by H. Pylori showed a higher efficacy than VPZ (95.8%) as compared to PPI (69.6%). In another RCT, adverse effects including diarrhea, nausea and body rash were observed in 32.7% of the people taking VPZ as compared to 40.5% of the people taking PPI. VPZ was shown to be much more cost effective as compared to PPI.

This article concludes that VPZ is superior to PPI in terms of efficacy, safety and cost-effectiveness in reflux disorders and H. pylori eradication. Hence, use of vonoprazan should be preferred over conventional PPIs in these disorders. As most of the research was conducted in Japan, studies should be carried out in different regions of the world to explore if these results are extrapolated in those regions. Research is also needed to explore the efficiency of VPZ in scenarios of PPI resistance.

1. Introduction

Gastroesophageal reflux diseases and H. pylori-induced duodenal and gastric ulcers are some of the most prevalent medical conditions worldwide, with a prevalence rate reported to be 10–20% [1,2]. Most of the patients affected with H. Pylori have no symptoms, but the infection can lead to peptic ulcers, MALToma and adenocarcinoma of the stomach [2]. Chronic untreated reflux diseases can cause a variety of conditions including esophagitis, Barrett's esophagus, esophageal carcinoma, gastric ulcers, and even life-threatening esophageal and gastric perforation [3–7]. Studies have shown that these complications can be avoided or minimized by agents that work by neutralizing the acidic pH of the stomach [8] (see Fig. 1)

Different classes of medications are used to decrease the gastric pH including Proton pump inhibitors (PPIs), H2 Histamine blockers, antacids etc. The most commonly used among these are PPIs, which are also a part of combination drugs used for H. Pylori eradication therapy. However, up to 40% of people with gastroesophageal reflux diseases have reported at least some resistance to conventional PPI therapy. The mechanisms of this resistance are thought to be poor control of gastric acid secretion, esophageal hypersensitivity, and changes in the esophageal epithelium [9]. Recently, a new drug, Vonoprazan (aka TAK-438), has been approved for clinical use in Japan to reduce intragastric pH [10,11]. VPZ is a potassium-competitive acid blocker (P-CAB) which works by inhibiting potassium ion binding to the H+/K + -ATPase channel in the gastric parietal cells. VPZ appears to be superior to PPIs in the sense that VPZ does not depend upon gastric acid activation to inhibit acid secretion and has a longer half-life [12,13].

Recent literature has reported that the rate of gastroesophageal reflux disease treatment and H. Pylori eradication is higher with VPZ as

* Corresponding author.
E-mail addresses: dr.shery260@gmail.com (M. Shehryar), ranauzair503@gmail.com (R.U. Ahmad), hira.kkareem@gmail.com (H.K. Kareem), zahraayat590@gmail.com (L. Khan), fawad1110@gmail.com (M.F. Ashraf), Ahtizaz786@gmail.com (A. Hassan), Sabeenasaeed3335@gmail.com (S. Saeed), haseebkhantareen80@gmail.com (H.K. Tareen), adnazir@gmail.com (D.A. Nazir), aizazashrafkhan@outlook.com (M.A. Ashraf).

https://doi.org/10.1016/j.amsu.2022.104760
Received 5 July 2022; Received in revised form 18 September 2022; Accepted 19 September 2022
Available online 22 September 2022
2049-0801/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

compared to conventional PPI therapy [14,15]. So the use of vonoprazan should be preferred over conventional therapy of PPIs used in gastro-intestinal reflux diseases and eradication of H. Pylori. But vonoprazan is still a relatively new drug and the literature is a bit inconclusive about its efficacy in cases of PPI resistance. So further research is needed to explore the effectiveness of vonoprazan in cases of PPI resistance. Here we review whether VPZ is in fact superior to PPI therapy in PPI-resistant reflux diseases.

2. Methods

Literature was searched on PubMed. MeSH keywords used were ‘‘vonoprazan, vonoprazan vs PPIs, efficacy of vonoprazan, safety and cost effectiveness of vonoprazan, and Proton Pump Inhibitors (PPIs)’’.

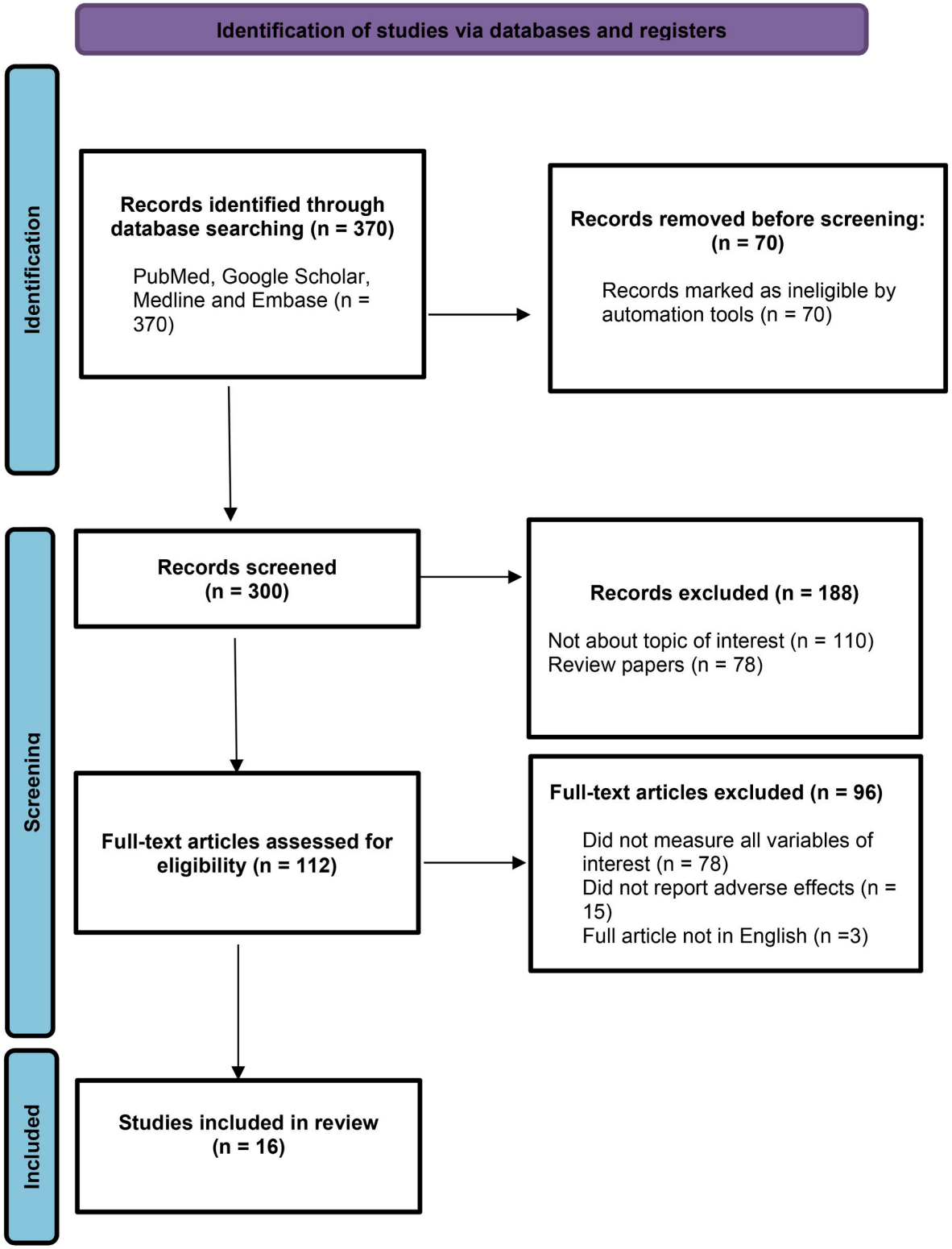

Fig. 1. Prisma flowchart.

Studies were selected after applying the following inclusion/exclusion criteria. The inclusion criteria were: 1) Human subjects; 2) Papers published in the English language; 3) Study types that are RCT's. The exclusion criteria were: 1) Non-English literature.

3. Results

After applying the MeSH keywords, a total of 370 articles were obtained. Of these articles, 70 were removed as they were marked as ineligible by automation tools. 110 articles were removed as they didn't include a topic of interest and 78 were review articles. On secondary screening, 78 articles were not included as they didn't measure all variables of interest; 15 didn't report adverse effects, and 3 articles were not in English. The remaining 16 articles were used for our review article.

4. Discussion

4.1. Efficacy

4.1.1. Pre-clinical

In vitro and in vivo studies were done on the porcine stomach to observe the antacid secretory effect of vonoprazan and lansoprazole. pH was kept at 6–5 while the temperature was kept at 37° Celsius in an in vitro environment. The H+/K + ATPase inhibition was 400 times more than lansoprazole. While according to half lethal dose values in the in-vivo environment, vonoprazan was 1.2–2.0 times potent. Vonoprazan is unaffected by the change in pH, unlike lansoprazole, which makes it suitable for use in in-vitro and in-vivo environments, where the pH is neutral and highly acidic, respectively [16].

4.1.2. Clinical studies

4.1.2.1. GERD. It is caused by the rush of acidic stomach contents to the esophagus resulting in complications such as epithelial changes, etc. PPIs are the first-line treatment for GERD, although almost 30–40% of GERD patients are resistant to this therapy. For treatment of erosive esophagitis, the vonoprazan effect was observed using a double-blind method. 732 patients were examined endoscopically after taking 5,10,20 and 40 mg vonoprazan and 30 mg lansoprazole daily. Healing proportions at week 4 with vonoprazan 5,10,20 and 40 mg and 30 mg lansoprazole were 92.3, 92.5, 94.4, 97.0, and 93.2, respectively, which shows vonoprazan is superior to lansoprazole in all its effects [17].

4.1.2.2. Ulcers. Several randomized trials were conducted to determine the efficacy of vonoprazan versus esomeprazole in post-endoscopic submucosal dissection (post-ESD) artificial ulcers. After the 3rd day to 8th week of post-ESD, the P-2 group of patients with a total number of 92 patients was given vonoprazan 20 mg per day and esomeprazole 20 mg per day. Endoscopic results showed ulcer constriction of 94.9% with vonoprazan, which was higher than 78% with esomeprazole [18].

Another study shows the efficacy of vonoprazan, which included 35 patients, after treatment with ESD for gastric adenoma. These 35 patients were given 20 mg per day of vonoprazan for 4 weeks.

On the other hand, 33 patients were given esomeprazole 20 mg per day for the same duration. Efficacy of vonoprazan was much higher with an ulcer constriction rate of 97.7% while it was 94.5% with esomeprazole [19].

4.1.2.3. Helicobacter pylori eradication. A randomized trial on 141 patients with a positive history of H. -pylori shows significantly higher efficacy of the vonoprazan group. Eradication rate with the vonoprazan group (VPZ 20 mg, AMX 750 mg, and CLB 200–400 mg) was 95.8 and 95% while with PPI it was 69.6 and 95% in IIT analysis [20].

32 patients who had known cases of erosive esophagitis (EE) were given 20 mg per day of vonoprazan and 30 mg per day of lansoprazole in a randomized double-blind study for 14 days. Relief of heartburn occurs earlier with vonoprazan than with lansoprazole. Reported rates on day 1 were 31.3% and 12.5% with vonoprazan and lansoprazole, respectively. Both regimens were well tolerated [21].

A parallel-group comparison study was done in a double-blind manner in patients with EE who were endoscopically confirmed. 401 patients were observed for 8 weeks where 99% of patients were healed with vonoprazan while 95.5% were healed with lansoprazole, which shows that vonoprazan is not inferior to PPI's [22].

4.1.2.4. Gastric mucosal injury. 8 patients with gastric mucosal injury were included in the study. They were already taking standard PPI treatment along with pH monitoring. The patients were evaluated again after the prohibition of therapy and 20 mg per day of vonoprazan was followed afterward. Patients were not positive for H. -pylori infection or CYP2C19 metabolizers. In 87.5% of patients (n = 7) complete gastric mucosal healing takes place after therapy from vonoprazan [23].

4.1.2.5. Gastric or duodenal ulcer. 650 subjects were allowed to conduct a randomized, double-blind study. Out of 650 subjects, 641 received complete 1st-time therapy. The eradication rate with vonoprazan was 92.6% in first-line therapy as compared to 75.9% with lansoprazole, with the superiority of 16.7% to the vonoprazan group. Thus, vonoprazan is not inferior to PPIs. Both 1st& 2nd triple therapies were well tolerated [24].

Summary of these results are given in Table 1.

4.2. Safety

The first line of treatment for GERD is PPI, but in recent studies, 20 mg per day of vonoprazan is being compared to PPIs in their efficacy and safety along with adverse effects. To show that vonoprazan is non-inferior to PPIs, a direct comparison was done between both.

The risk ratio for PPI and vonoprazan comes to be 1.08 and 1.06, respectively. Keeping in view all the adverse effects and efficacy of both. Significantly, increased outcomes were observed for vonoprazan as compared to lansoprazole, where the value of the RR was 1.14 (1.06–1.22). It suggests that the safety results for vonoprazan are nearly equal to PPIs with increased efficacy for vonoprazan [25].

Analysis of vonoprazan was done as compared to PPIs for H. pylori eradication. In this study, great number of 14,636 patients were included. In first line therapies, the pooled ER of regimens that had vonoprazan was much higher than the regimens having PPI's in them along with per protocol analysis (89.0%–774.2%). In the clariythromycin-resistant and susceptible stains, much higher results were obtained with vonoprazan. As a part of 2nd line therapy vonoprazan did not show as superior to PPI's based on both intentions to treat (83.4% vs 82.0%) along with per protocol analysis (89.3% vs 90.1%). In the end, the safety of the vonoprazan regimen was calculated to be better than PPI's regimens (33.3% versus 26.4%). Safety is equal or greater than that of PPI's [26].

4.3. Adverse effects

A randomized controlled trial was conducted on 2715 patients having 63-plus age. They were given VPZ and analyzed versus the old regimen i.e., PPIs. 10 cases of diarrhea were reported. 6 cases of nausea, and 5 cases of body rash were observed. All these adverse effects were normal and were also observed with PPIs in conventional use [27].

Adverse events were also studied in two groups in patients with Helicobacter pylori eradication. Both groups were given VPZ and PPIs and adverse effects were observed for a pre-decided duration. The first group consisted of 897 patients with H. pylori infection. Eradication rates with VPZ and PPIs were 91.4% and 74.5% respectively, while the

Table 1
Efficacy of vonoprazan vs proton pump inhibitors in different clinical studies.

References	No. Of Subjects	Disease	Dose of vonoprazan	Efficacy of vonoprazan	Efficacy of PPIs
K. Ashida et al. (2015) [17]	732	EE	5,10, 20&40 mg	92.3–97%	93.2%
Tsuchiya et al. (2017) [18].	92	ESD	20 mg	94.9%	78%
Maruoka et al. (2017) [19]	35	ESD artificial ulcers	20 mg	97.7%	94.5%
Masafumi Maruyama et al. (2017) [20]	141	H. pylori infection	20 mg	95.8%	69.6%
Oshima et al. (2019) [22]	32	EE	20 mg	31.3%	12.5%
Ashida et al. (2016) [24]	401	EE	20 mg	99.0%	95.5%
Yamashita et al. (2017) [23]	8	Gastric Mucosal Injury	20 mg	87.5%	NIL
Kazunari Murakami et al. (2016) [24]	650	Gastric or Doudenal Ulcer	20 mg	92.6%	75.9%

adverse events came out to be 32.7% and 40.5% respectively in the first group, which indicates that VPZ has lesser adverse effects as compared to PPI while being more efficacious [28].

The other group had 141 patients with H. pylori infection. The adverse effects in this group came out to be 26.3% and 37.7% for VPZ and PPIs respectively. Eradication rates were 95.8% and 69.6% with VPZ and PPIs, respectively [20].

Summary of these studies on adverse effects is given in Table 2.

4.4. Cost effectiveness

Reflux esophagitis was treated with 30 mg lansoprazole therapy and 20 mg Vonoprazan in Japan and cost-effectiveness was analyzed for 12 months. Studies show that VPZ was more efficient in terms of cost-effectiveness as compared to lansoprazole i.e., 58 yen per day versus 68 yen per day, respectively [29].

Another cost-effectiveness study was done where the remission rate of erosive esophagitis was observed taking the cost of treatment under consideration. Intermittent PPI therapy using lansoprazole costs 39 Yen per day while Intermittent P-CAB therapy with vonoprazan costs 39 Yen per day. However, Maintenance therapy with Vonoprazan is more effective for reflux esophagitis, but it costs 185 Yen per day as compared to 122 Yen per day if we use PPI as Maintenance therapy [30].

Helicobacter eradication was treated with Rabeprazole triple therapy and the total cost was analyzed as compared to Vonoprazan triple therapy. Triple therapy included VPZ or RPZ with Amoxicillin and Clarithromycin. This retrospective study was done in Japan's Yasaku on 209 patients. The cost-effective ratio was determined that came to be 360.1 and 379.4 Japanese Yen for Vonoprazan triple therapy and Rabeprazole triple therapy, respectively [31]. Summary of these clinical studies on cost effectiveness is given in Table 3.

Although this review was comprehensive, results of this article have to be seen in the light of some limitations. The first limitation is the inadequate sample size of most of the included RCTs. Future trials should be conducted on a larger group of people and multiple health centers have to be included to increase the scope and generalized effects of the results. Another major limitation is that all the studies included in the cost-effectiveness portion were conducted in Japan only. Although these studies were conclusive and comprehensive as the cost can be applied to other currencies as well but still more studies have to be conducted in other countries to ascertain worldwide generalized results. Further studies should address this issue. There are some limitations like different studies had, different periods of follow up and different modes of interventions as well, which may have influenced the results.

Table 2
Comparison of Adverse Effects of VPZ vs PPIs in H. pylori Eradication.

No with patients	disease	ER VPZ	ER PPI's	Adverse events VPZ	PPI's	References
897	H. pylori eradication	91.4%	74.8%	32.7%	40.5%	Qiu-Ju Lyu et al. (2019) [28]
141	H. pylori eradication	95.8%	69.6%	26.3%	37.7%	Masafumi Maruyama et al. (2017) [20]

H. pylori eradication [n = 14,636 patients]		VPZ	PPI'S
FIRST LINE TREATMENT	Pooled eradication rate	85.0%	68.0%
	Per protocol analysis	89.0%	74.2%
SECOND LINE TREATMENT	Pooled eradication rate	83.4%	82.0%
	Per protocol analysis	89.3%	90.1%
	Safety	33.3%	26.4%

Table 3
Comparison of Cost Effectiveness of VPZ vs PPIs.

Disease	CEO of VPZ	CER of PPI's	References
Reflux esophagitis	58 YEN/ DAY	68 YEN/ DAY	Habu et al. (2019) [29].
Reflux esophagitis	31 YEN/ DAY	39 YEN/ DAY	Yasuku Habu et al. (2021) [30]
H. pylori eradication	360.1 JPY/ %	379.4 JPY/ %	Kajihara et al. (2017) [31]

5. Conclusion

This review article suggests that Vonoprazan is 400 times more efficacious than PPI use as proven in pre-clinical studies because it doesn't get affected by pH changes. We further showed that in clinical studies done with VPZ on GERD, esophagitis and gastric or duodenal ulcers, VPZ has been found to be more potent. Also, this paper shows that while being more efficient, the safety profile of Vonoprazan in Reflux Gastritis is just similar to that of PPI use, with no clinically significant difference in safety. However, evidence suggests that in the case of H. pylori eradication therapy, Vonoprazan is safer than PPI with less conventional PPI-related adverse effects in VPZ usage. Our article suggests that VPZ is cost-effective as compared to PPI's. But we further elaborated that the use of P-CAB intermittently was found to be more cost-effective for both reflux esophagitis patients and H. pylori eradication. But, a more effective strategy in case of treating reflux esophagitis is to continue maintenance dose of PPI or P-CAB, which is costly with P-CAB compared to PPI.

Ethical approval

Not required.

Sources of funding

None.

Author contribution

All authors contributed towards data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Trail registry number

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Haseeb Khan Tareen.

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, **the Editor in Chief** must be made aware of all such conditions.

Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

Not required.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Annals of medicine and surgery

The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Declaration of competing interest

None.

References

[1] J. Dent, H.B. El-Serag, M. Wallander, S. Johansson, Epidemiology of gastro-oesophageal reflux disease: a systematic review, Gut 54 (5) (2005 May 1) 710–717.

[2] B.B. de Brito, F.A.F. da Silva, A.S. Soares, V.A. Pereira, M.L.C. Santos, M. M. Sampaio, P.H.M. Neves, F.F. de Melo, Pathogenesis and clinical management of *Helicobacter pylori* gastric infection, World J. Gastroenterol. 25 (37) (2019 Oct 7) 5578–5589.

[3] S.J. Spechler, R.K. Goyal, Barrett's esophagus, N. Engl. J. Med. 315 (6) (1986 Aug 7) 362–371.

[4] A.C. Ford, D. Forman, R.H. Hunt, Y. Yuan, P. Moayyedi, Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials, Br. Med. J. (2014 May 20) 348.

[5] K. Fukase, M. Kato, S. Kikuchi, K. Inoue, N. Uemura, S. Okamoto, S. Terao, K. Amagai, S. Hayashi, M. Asaka, Japan Gast Study Group, Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial, Lancet 372 (9636) (2008 Aug 2) 392–397.

[6] S.B. Yoon, J.M. Park, C.H. Lim, Y.K. Cho, M.G. Choi, Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis, Helicobacter 19 (4) (2014 Aug) 243–248.

[7] A.C. Ford, B. Delaney, D. Forman, P. Moayyedi, Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients, Cochrane Database Syst. Rev. (2) (2006).

[8] D.Y. Graham, History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer, World J. Gastroenterol.: WJG 20 (18) (2014 May 14) 5191.

[9] N.J. Bell, D. Burget, C. Howden, J. Wilkinson, R.H. Hunt, Appropriate acid suppression for the management of gastro-oesophageal reflux disease, Digestion 51 (1) (1992) 59–67.

[10] M. Cicala, S. Emerenziani, M.P. Guarino, M. Ribolsi, Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease, World J. Gastroenterol.: WJG 19 (39) (2013 Oct 21) 6529.

[11] M. Kondo, M. Kawamoto, A. Hasuoka, M. Kajino, N. Inatomi, N. Tarui, High-throughput screening of potassium-competitive acid blockers, J. Biomol. Screen 17 (2) (2012 Feb) 177–182.

[12] K.P. Garnock-Jones, Vonoprazan, First global approval, Drugs 75 (4) (2015 Mar) 439–443.

[13] M. Sugimoto, T. Furuta, N. Shirai, M. Kajimura, A. Hishida, M. Sakurai, K. Ohashi, T. Ishizaki, Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status, Clin. Pharmacol. Ther. 76 (4) (2004 Oct) 290–301.

[14] D.R. Scott, K.B. Munson, E.A. Marcus, N.W. Lambrecht, G. Sachs, The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+-ATP ase. Alimentary pharmacology & therapeutics 42 (11–12) (2015 Dec) 1315–1326.

[15] S. Kiyotoki, J. Nishikawa, I. Sakaida, Efficacy of vonoprazan for helicobacter pylori eradication, Intern. Med. 59 (2) (2020 Jan 15) 153–161.

[16] X.Y.-Q. Li, Vonoprazan; A novel and potent alternative in the treatment of acid related diseases, Dig. Dis. Sci. (2017).

[17] K. Ashida, S. Y, Randomized clinical trial; a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs lansoprazole for the treatment of erosive esophagitis, Aliment Pharmacol. Therapeut. (2015) 685–695.

[18] I. Tsuchiya, Effect of vonoprazan on the treatment of artificial gastric ulcers after endoscopic submucosal dissection; prospective randomized controlled trial, National Library of Medicine (2017).

[19] D. Maruoka, Vonoprazan is superior to proton pump inhibitors in healing artificial ulcers of stomach post-endoscopic submucosal dissection; A propensity score matching analysis, National Library of Medicine (2017).

[20] N.T. Masafumi Maruyama, The vonoprazan-based regimen is more useful than the PPI-based one for first-line Helicobacter pylori eradication; A Randomized Controlled Trial. Canadian, J. Gastroenterol. Hepatol. (2017).

[21] T. Oshima, Randomized clinical trial; vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive esophagitis, National Library of Medicine (2019).

[22] K. Ashida, Randomized clinical trial; vonoprazan, a novel potassium competitive acid blocker, vs. lansoprazole for the healing of erosive esophagitis, National Library of Medicine (2016).

[23] H. Yamashita, The effects of switching to vonoprazan, a novel competitive acid blocker, on gastric acidity and reflux patterns in patients with erosive esophagitis refractory to proton pump inhibitors, National Library of Medicine (2017).

[24] Y.S. Kazunari Murakami, Vonoprazan, a novel potassium competitive acid blocker, as a component of the first-line and second-line triple therapy for Helicobacter pylori eradication; a phase 3, randomized double-blind study, Gut (2016) 1439–1446.

[25] Y. Cheng, Direct comparison of the efficacy and safety of vonoprazan versus proton pump inhibitors for gastroesophageal reflux disease; a systemic review and meta-analysis, National Library of Medicine (2021).

[26] S.Q. Dong, Review; A Japanese population-based meta-analysis of von Drazan versus PPI for Helicobacter pylori eradication therapy; Is superiority an illusion/, National Library of Medicine (2017).

[27] S. Shichijo, Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori; A multicenter retrospective study in clinical practice, National Library of Medicine (2016).

[28] Q.-H.P.-F. Qiu-Ju Lyu, Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for Helicobacter pylori eradication; A meta-analysis of randomized clinical trials, BioMed Res. Int. (2019).

[29] Y. Habu, Vonoprazan versus Lansoprazole for the initial treatment of Reflux Esophagitis; A cost-effectiveness analysis in Japan, National Library of Medicine (2019).

[30] R.H. Yasuku Habu, Treatment strategies for reflux esophagitis including a potassium-competitive acid blocker; A cost-effectiveness analysis in Japan, Journal of General and Family Medicine (2021).

[31] Y. Kajihara, Analysis of cost-effectiveness of using vonoprazan-amoxicillin-clarithromycin in triple therapy for first-line Helicobacter pylori eradication, National Library of Medicine (2017).