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Effectiveness and Safety of Vonoprazan versus Proton Pump Inhibitors for Second-Line *Helicobacter pylori* Eradication Therapy: Systematic Review and Meta-Analysis

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Keywords
Helicobacter pylori · Proton pump inhibitor · Potassium-competitive acid blocker · Outcome measure · Therapeutics

Abstract
Background: A novel potassium-competitive acid blocker, vonoprazan (VPZ), improves first-line *Helicobacter pylori* eradication success. The aim of this systematic review is to clarify the effectiveness and safety of second-line *H. pylori* eradication therapy comparing VPZ and proton pump inhibitor (PPI)-based regimens. ***Methods:*** Medline (PubMed), EMBASE, Web of Science, Cochrane Library, and the Japan Medical Abstract Society Database were searched. ***Results:*** We selected 16 studies for quantitative review. Forest plot analysis showed significant superiority of VPZ over PPI-based regimens in overall second-line *H. pylori* eradication success (OR 1.51, 95% CI 1.27–1.81, $p < 0.001$). Forest plots from 2 studies with propensity score matched analysis showed significant superiority of VPZ over PPI-based regimens (OR 3.09, 95% CI 1.71–5.58, $p < 0.001$). The remaining 14 studies with per-protocol analysis and the full analysis set also showed significant superiority (OR 1.40, 95% CI 1.16–1.69, $p < 0.001$). Regarding adverse events, Forest plot analysis did not show a significant difference between the 2 regimens (OR 0.88, 95% CI 0.58–1.32, $p = 0.53$). ***Conclusions:*** A VPZ-based regimen has significant superiority over a PPI-based regimen for second-line *H. pylori* eradication therapy. A VPZ-based second-line *H. pylori* eradication regimen can be the first choice.

Introduction

Helicobacter pylori infection is a major risk factor for the development of gastric cancer and the estimated number of new cases and deaths from gastric cancer worldwide in 2018 are 1,033,700 and 782,700, respectively [1]. A recent pooled data meta-analysis clearly showed that *H. pylori* eradication decreases the incidence of gastric cancer [2]. Therefore, successful eradication of *H. pylori* is the most important strategy to prevent gastric cancer worldwide.

A novel potassium-competitive acid blocker, vonoprazan (VPZ), was made available in Japan in 2015 as part of a standard triple-drug *H. pylori* eradication regimen. The

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Japanese health insurance system approves standard triple therapy including amoxicillin, clarithromycin, and a VPZ or proton pump inhibitor (PPI) twice daily for 7 days as first-line therapy and amoxicillin, metronidazole, and VPZ or PPI twice daily for 7 days as second-line therapy. A VPZ has a significantly higher acid suppression effect by direct inhibition of H^+-K^+ exchange [3]. One of the key elements of successful eradication is maintenance of ambient pH elevation for 24 h with an acid suppressing drug. A randomized controlled trial showed superior first-line *H. pylori* eradication success of a VPZ-based regimen over a PPI-based regimen [4]. Also, recent systematic reviews confirm the superiority of success in first-line eradication [5, 6]. Although previous systematic reviews did not show significant superiority of a VPZ-based regimen over a PPI-based regimen in second-line eradication, the number of patients and studies were insufficient to appropriately evaluate a difference of eradication success between the 2 regimens. This study aims to clarify the effectiveness and safety of a VPZ-based regimen compared with a PPI-based regimen as second-line *H. pylori* eradication therapy.

Methods

This study is registered in the International Prospective Register of Systematic Review (PROSPERO) according to protocol (Registration ID: CRD42019132545). It includes both randomized controlled studies and cohort studies that compared VPZ-based with PPI-based regimens as second-line *H. pylori* eradication therapy. The primary outcome is the rate of eradication success in second-line *H. pylori* eradication therapy, and a secondary outcome is the rate of adverse events.

Search Strategy

On July 22, 2019, Medline (PubMed), EMBASE, Web of Science, and Cochrane Library were searched using the following key words: "vonoprazan or potassium-competitive acid blocker and PPI and *H. pylori*". The Japan Medical Abstract Society Database was also searched. Languages were limited to English and Japanese. We included only published articles.

Study Selection

Two authors (S.S. and Y.K.) independently searched and reviewed the titles and abstracts of articles. After selection, full text screening was independently performed. Duplicated studies were excluded. In case of disagreement, the 2 authors discussed the study with a third author to reach a consensus.

Data Extraction and Quality Assessment

We abstracted the following data from published articles: study design, year of publication, study period, country, number of patients, eradication success, adverse events, type of PPI used as second-line eradication therapy, and type of acid blocker (VPZ or PPI) used in failed first-line eradication therapy. When both propensity score matched and per-protocol analyses were reported in one article, we abstracted the data of the propensity score matched analysis. After the first author abstracted the data, the second author verified the data. When critical data were unclear, we contacted the corresponding author and requested further information.

Risk of Bias

We used the risk of bias assessment tool for non-randomized studies including selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting [7].

Statistical Analysis

To evaluate the efficacy and safety of an intervention, we used Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled OR with 95% CI was calculated. The Mantel-Haenszel fixed effect model was used as all studies were reported from Japan and used almost the same antibiotics. Interstudy heterogeneity was evaluated with the chi-square test and I^2 Higgins's classification [8]. I^2 values of 25, 50, and 75% were considered as low, moderate, and high heterogeneity, respectively.

Results

Study Selection

The selection of studies for systematic review is shown in Figure 1. The first search identified 328 studies, and then 16 studies [9–24] were selected after excluding 312 studies. Unlike first-line *H. pylori* eradication therapy, no randomized-controlled study of second-line eradication therapy has been reported. Therefore, all 16 studies including 6,664 patients are observational studies.

Characteristics of Studies

All studies originated from Japan where the health insurance system has reimbursed for VPZ-based *H. pylori* eradication therapy since 2015 (Table 1). All studies used a second-line standard triple regimen including amoxicillin 750 mg, metronidazole 250 mg, and acid blocker (VPZ 20 mg, esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, or rabeprazole 10 mg) twice daily for 7 days. Of the 16 selected studies, 7 (44%) [9, 12–16, 19] were written in Japanese. Selected studies included one prospective study [20] and 15 retrospective studies. Two of the 16 studies used propensity score matched analysis [19, 22]. In the remaining 14 studies, one study used a full analysis set [18]. Although the type of potassium-competitive acid blocker used in second-line therapy was VPZ in all studies, various PPIs were used as second-line therapy.

The type of acid blocker used as failed first-line therapy was reported in only 3 of 16 studies (19%) [12, 14, 22]. All patients with a PPI-based regimen as second-line therapy

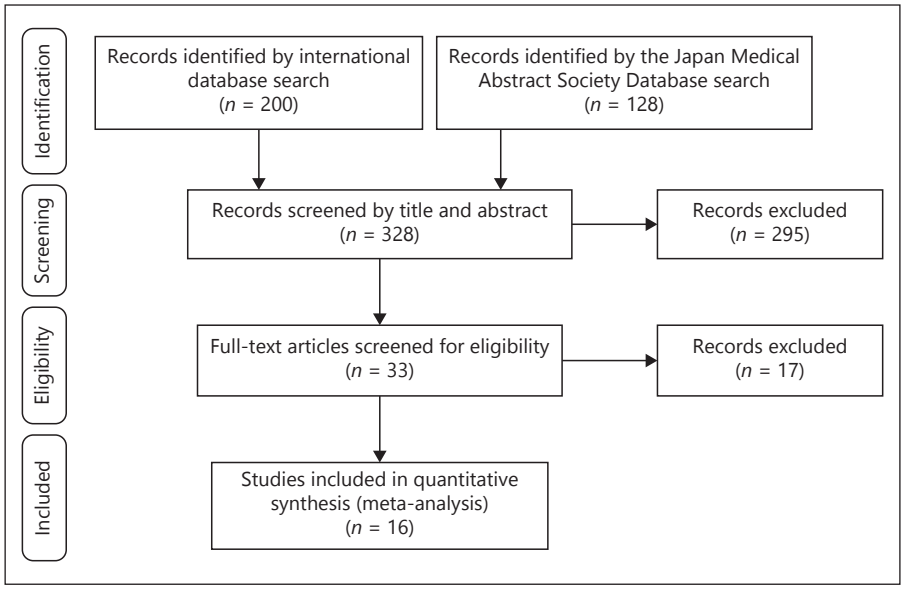

Fig. 1. Study flowchart.

Table 1. Characteristics of 16 studies included in this meta-analysis

First author [reference]	Year	VPZ-based regimen	PPI-based regimen	Type of PPI used as 2nd-line	Type of acid blocker used as failed 1st line (2nd: VPZ)	Type of acid blocker used as failed 1st line (2nd: PPI)	Adverse events
Saegusa [9]	2016	20	27	RPZ	NR	NR	NR
Tsujimae [10]	2016	45	51	EPZ	NR	NR	NR
Yamada [11]	2016	61	374	EPZ, LPZ, RPZ	NR	NR	NR
Yoshida [12]	2016	34	56	EPZ, LPZ, RPZ	VPZ 13, PPI 21	PPI only	NR
Yoshizumi [13]	2016	27	214	EPZ, LPZ, RPZ	NR	NR	NR
Ishihara [14]	2017	20	13	EPZ, LPZ	VPZ 14, PPI 6	PPI only	NR
Mukai [15]	2017	40	24	NR	NR	NR	Reported
Murai [16]	2017	73	147	EPZ, LPZ, OPZ, RPZ	NR	NR	NR
Nishizawa [17]	2017	63	529	LPZ, RPZ	NR	NR	Reported
Sakurai [18]	2017	76	185	EPZ, LPZ, RPZ	NR	NR	Reported
Sato [19]	2017	100	100	NR	NR	NR	NR
Sue [20]	2017	211	145	EPZ, LPZ, OPZ, RPZ	NR	NR	Reported
Kusunoki [21]	2019	48	108	EPZ, LPZ, RPZ	NR	NR	NR
Nabeta [22]	2019	274	274	LPZ, RPZ	PPI only	PPI only	Reported
Mori [24]	2019	1,147	2,051	EPZ, LPZ, OPZ, RPZ	NR	NR	NR
Saito [23]	2019	54	73	EPZ	NR	NR	NR

VPZ, vonoprazan; PPI, proton pump inhibitor; NR, not reported; EPZ, esomeprazole; LPZ, lansoprazole; OPZ, omeprazole; RPZ, rabeprazole.

had taken a PPI-based regimen as failed first-line therapy. Except for one study [22], patients using a VPZ-based regimen as second-line therapy had a trend of receiving a VPZ-based regimen as failed first-line therapy (Table 1).

Risk of Bias

The risk of bias assessments is shown in Table 2. Except for one prospective study [20], the remaining 15 retrospective studies used historical controls.

Second-Line H. pylori *Eradication Success Rate*

We included 16 studies to clarify the success rate of second-line eradication therapy (Fig. 2). Forest plot analysis showed significant superiority of VPZ over PPI-based regimens in the overall second-line *H. pylori* eradication success (OR 1.51, 95% CI 1.27–1.81, $p < 0.001$) without heterogeneity ($I^2 = 0\%$). Grossly, the overall eradication success rates were 91 and 88%, respectively.

Table 2. Risk of bias assessment tool for non-randomized studies

First author [reference]	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Saegusa [9]	High	High	Low	Low	Unclear	Unclear
Tsujimae [10]	High	High	Low	Low	Unclear	Unclear
Yamada [11]	High	High	Low	Low	Unclear	Unclear
Yoshida [12]	High	High	Low	Low	Unclear	Unclear
Yoshizumi [13]	High	High	Low	Low	Low	Unclear
Ishihara [14]	High	High	Low	Low	Low	Unclear
Mukai [15]	High	High	Low	Low	Low	Low
Murai [16]	High	High	Low	Low	Low	Unclear
Nishizawa [17]	High	High	Low	Low	Unclear	Low
Sakurai [18]	High	High	Low	Low	Unclear	Low
Sato [19]	High	Low	Low	Low	Low	Unclear
Sue [20]	Low	High	Low	Low	Low	Low
Kusunoki [21]	High	High	Low	Low	Unclear	Unclear
Nabeta [22]	High	Low	Low	Low	Low	Low
Mori [24]	High	High	Low	Low	Low	Unclear
Saito [23]	High	High	Low	Low	Unclear	Unclear

Two studies with propensity score matched analysis were separately analyzed. In propensity score matched analyses, 2 studies showed significant superiority of VPZ-based over PPI-based regimens (OR 3.09, 95% CI 1.71–5.58, $p < 0.001$). In per-protocol analysis and the full analysis set, the remaining 14 studies supported the superiority of VPZ-based regimens (OR 1.40, 95% CI 1.16–1.69, $p < 0.001$). Despite the significant difference between the 2 regimens in this meta-analysis, only 2 studies with propensity score matched analysis and one study with per-protocol analysis independently showed a significant difference between VPZ and PPI-based regimens (Fig. 2).

Adverse Events

Five of the 16 studies (31%) reported adverse events, and there were no significant differences in incidence between the 2 regimens (OR 0.88, 95% CI 0.58–1.32, $p = 0.53$) with low heterogeneity ($I^2 = 10\%$; Fig. 3). Two of 5 studies reported the nature of the adverse events such as diarrhea, soft stool, nausea, or rash [18, 22].

Discussion

This systematic review shows significant superiority of VPZ over PPI-based regimens for the success of second-line *H. pylori* eradication. The frequency of adverse events was similar for both regimens. The strong and homogenous acid suppression effect of VPZ may explain the success of second-line eradication. A key element for successful eradication is maintenance of gastric pH >4.0 [25], and VPZ 40 mg daily can maintain pH >4.0 for >90% of the day [26]. Several recent studies reported that VPZ-based regimens as first-line eradication therapy improved eradication success. Nevertheless, 5–15% of patients suffered therapeutic failures leading to the need for second-line eradication therapy [5]. Second-line eradication success is as important as first-line success. At this time, third-line eradication therapy is not reimbursed by the Japanese health insurance system and there is no defined regimen. Undoubtedly, second time failure discourages both patients and health care providers. To decrease the failure rate, we recommend including VPZ in the second-line eradication regimen.

A recent systematic review reported similar second-line eradication success comparing VPZ with PPI-based regimens [5]. Overall, 13 of the 16 studies in this meta-analysis did not show statistically significant differences between the 2 groups independently, but 11 of the 13 studies had a trend toward superiority of a VPZ-based regimen over a PPI-based regimen. We suggest 2 explanations why the results of the present systematic review were not consistent with a previous systematic review [5]. First, the number of studies and patients in the present study were much greater than in the previous systematic review [5]. Second, we included 2 large studies with propensity score matched analysis, and these studies may decrease the influence of confounding variables.

The success rates for first-line VPZ and first-line PPI eradication are approximately 89 and 74%, respectively [5], a larger difference than was shown with second-line

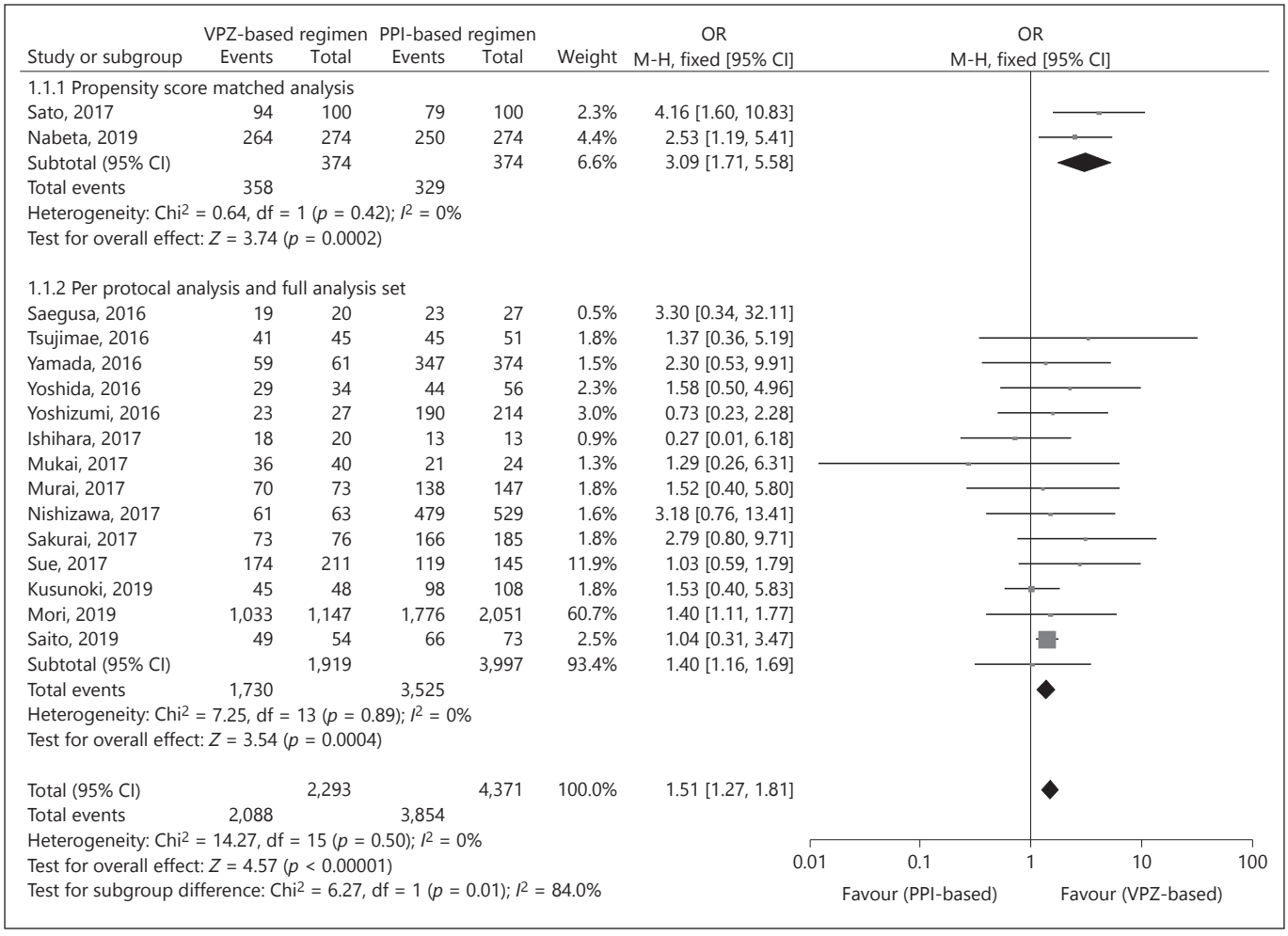

Fig. 2. Forest plot of second-line *H. pylori* eradication success comparing potassium-competitive acid blocker-based regimens with PPI-based regimens. VPZ, vonoprazan; PPI, proton pump inhibitor.

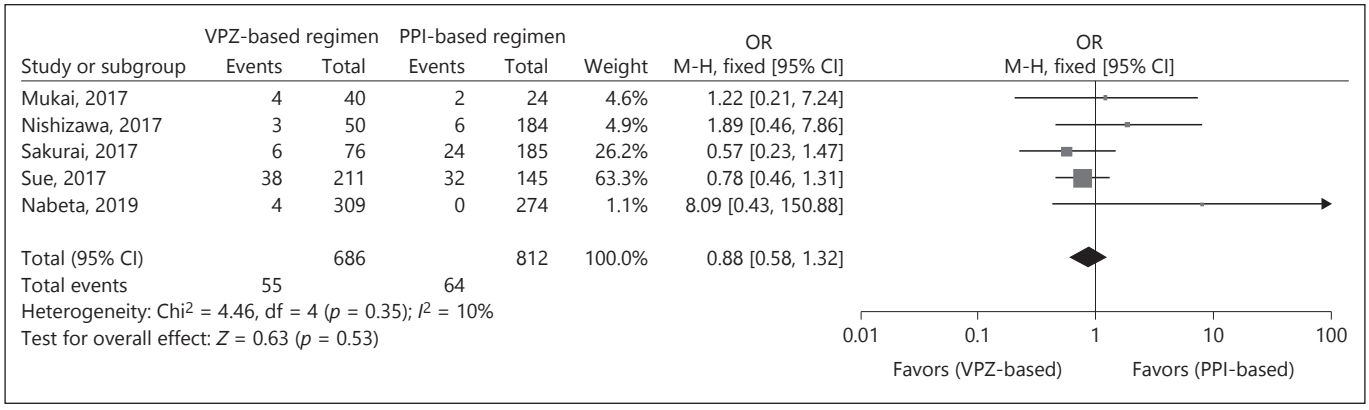

Fig. 3. Forest plot of adverse events of second-line *H. pylori* eradication therapy comparing potassium-competitive acid blocker-based regimens with PPI-based regimens. VPZ, vonoprazan; PPI, proton pump inhibitor.

eradication therapy in this systematic review (91 and 88%, respectively). The prevalence of clarithromycin-resistant *H. pylori* is increasing in Japan, and it has a remarkably decreased success rate of eradication with first-line PPI-based therapy. A low gastric pH is associated with enhanced clarithromycin resistance. Sahara et al. [27] evaluated gastric pH among patients receiving PPI twice daily, and it was much lower in patients with extensive metabolism of CYP2C19 than those with weaker metabolism. Saito et al. [28] reported that the rate of successful eradication in patients with extensive metabolism of CYP2C19 (52%) is much lower than those with weaker metabolism (85%). Taken together, low gastric pH in patients with extensive metabolism of CYP2C19 may be at least partially responsible for unsuccessful first-line *H. pylori* eradication therapy. Heterogenous effects of acid suppression by PPIs among the CYP2C19 genotype may lead to different success rates for eradication, especially in Japanese patients. Recently, strong and homogenous acid inhibition with VPZ-based regimens overcame these difficulties and increased the success of first-line eradication compared with PPI-based regimens [29]. Unlike clarithromycin and amoxicillin, metronidazole is stable regardless of ambient pH [30]. Therefore, the difference in second-line eradication success between VPZ and PPI-based second-line regimens may be smaller than for first-line therapy. In Japan, the prevalence of metronidazole resistant *H. pylori* (2%) is much less than that for clarithromycin (36%) [31]. VPZ-based regimens containing metronidazole and amoxicillin may remarkably improve eradication success in other countries with a high prevalence of metronidazole-resistant *H. pylori* (21–76%) [31, 32].

The rate of adverse events for second-line eradication therapy is about 8% in both groups in this study, which is less than for first-line eradication therapy. Amoxicillin is commonly used in both first- and second-line regimens. If moderate or severe adverse events such as a rash occur with failed first-line therapy, a second-line regimen including amoxicillin will not be used. Therefore, during second-line therapy, patients with a penicillin allergy might unintentionally be excluded.

We recognize some limitations in this meta-analysis. First, all studies originated from Japan and about half of them were written in Japanese. Second, no randomized controlled studies are included. Furthermore, 15 of 16 studies were retrospective and used historical controls with a time-frame shift between the 2 groups. Third, CYP2C19 and CYP3A4 genotypes were not evaluated. Fourth, metronidazole and penicillin resistance were not assessed. Fifth, the antibiotics used in failed first-line eradication therapy were not uniform except in one study [22]. Therefore, future large randomized controlled studies are necessary including patients with a history of failed VPZ-based first-line therapy.

In conclusion, a VPZ-based regimen has significant superiority over a PPI-based regimen as second-line *H. pylori* eradication therapy. The frequency of adverse events in the 2 groups is similar. We believe that a VPZ-based regimen is the first choice for the second-line *H. pylori* eradication therapy as well as first-line therapy.

Disclosure Statement

S.S. and H.Y. has received honoraria from Takeda Pharmaceutical. H.O. has received honoraria from Takeda and Otsuka Pharmaceuticals. All other authors declare no conflicts of interest regarding this study.

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None.

Author Contributions

S.S.: conception and design, data collection, data analysis and interpretation, drafting the manuscript, writing the manuscript, final approval of the manuscript. Y.K.: data collection, data analysis and interpretation, final approval of the manuscript. H.O.: writing the manuscript, data analysis and interpretation, final approval of the manuscript. H.S., Y.H., H.Y.: data analysis and interpretation, final approval of the manuscript. A.L.: writing the manuscript, final approval of the manuscript.

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