Impact of Vonoprazan Triple-Drug Blister Packs on H. pylori Eradication Rates in Japan: Interrupted Time Series Analysis

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ORIGINAL RESEARCH

Impact of Vonoprazan Triple-Drug Blister Packs on *H. pylori* Eradication Rates in Japan: Interrupted Time Series Analysis

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ABSTRACT

Introduction: *Helicobacter pylori* eradication therapy requires a complex prescribing schedule combining clarithromycin, amoxicillin, and a proton-pump inhibitor (PPI) or potassium-competitive acid blocker (P-CAB, vonoprazan). To reduce the burden of complex prescribing and increase adherence, a vonoprazan triple-drug blister pack comprising all three medications was launched in June 2016. This study aimed to assess the impact of the combination blister pack on eradication success rate in Japan immediately after launch.

Methods: We performed an interrupted time series analysis using a large administrative claims database of 7,300,000 insured individuals. We identified 36,570 patients who received first-line clarithromycin triple therapy from June 2015 to May 2016 (prelaunch) and 35,721 who received the same therapy from July 2016 to June 2017 (post-launch). The primary outcome was the success rate of clarithromycin triple therapy and the secondary outcomes were proportion of vonoprazan use and proportion of combination blister pack use.

Results: The success rate of clarithromycin triple therapy increased by 2.44% (95% confidence interval [CI] 1.36–3.52; $P < 0.0001$) after the launch of the vonoprazan triple-drug blister pack. The proportion of vonoprazan use and proportion of combination blister pack use increased by 12.7% (95% CI 10.0–15.3; $P < 0.0001$) and 29.2% (95% CI 25.4–32.9; $P < 0.0001$), respectively.

Conclusions: Launch of the vonoprazan triple-drug blister pack had a significant impact on the success rate of clarithromycin triple therapy, with greater proportions of vonoprazan and combination blister pack use. Introducing an easy-to-use formulation may be effective in changing prescribing practice and subsequent patient outcomes.

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Keywords: Drug packaging; Drug therapy; *Helicobacter pylori*; Interrupted time series analysis; Proton-pump inhibitors

Key Summary Points

Why carry out this study?

H. pylori eradication therapy requires a complex prescribing schedule combining clarithromycin, amoxicillin, and a proton-pump inhibitor or a potassium-competitive acid blocker such as vonoprazan

To reduce the burden of complex prescribing and increase adherence, a vonoprazan triple-drug blister pack comprising all three medications was launched in June 2016

This study aimed to assess the impact of the combination blister pack on eradication success rate in Japan immediately after launch through analysis of a large administrative claims database

What was learned from the study?

The success rate of clarithromycin triple therapy increased by 2.44% after launch of the vonoprazan triple-drug blister pack. The proportion of vonoprazan use and proportion of combination blister pack use increased by 12.7% and 29.2%, respectively

Launch of the vonoprazan triple-drug blister pack had a significant impact on the success rate of clarithromycin triple therapy, with greater proportions of vonoprazan and combination blister pack use. Introducing an easy-to-use formulation may be effective in changing prescribing practice and subsequent patient outcomes

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14547465.

INTRODUCTION

Helicobacter pylori affects 50% of the world's population and is associated with peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and stomach cancer [1–6]. Clinical practice guidelines recommend *H. pylori* eradication for patients with peptic ulcers and MALT lymphoma [4–6]. Moreover, several randomized controlled trials (RCTs) and meta-analyses have shown that eradication therapy reduces the risk of developing gastric cancer [7–16].

Clarithromycin triple therapy, comprising a proton-pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole, is the most common *H. pylori* eradication regimen worldwide [5]. However, the success rate of clarithromycin triple therapy has been declining with the rise in clarithromycin-resistant *H. pylori* [17–20]. Vonoprazan is a potassium-competitive acid blocker (P-CAB) launched in February 2015. It demonstrated noninferiority in a double-blind, randomized, phase 3 trial and subsequent superiority in an additional analysis versus lansoprazole; eradication rates were 92.6% (95% confidence interval [CI] 89.2–95.2) vs. 75.9% (95% CI 70.9–80.5), respectively [21].

Clarithromycin triple therapy requires a complex prescribing schedule. To reduce the burden of complex prescribing and increase drug compliance, combination blister packs of clarithromycin triple therapy, which include a PPI (lansoprazole or rabeprazole), were introduced in Japan by 2014. Subsequently, a triple-drug blister pack including vonoprazan (VONOSAP®) was launched on June 7, 2016, so that complex eradication therapy could be easily and accurately administrated [22].

In vonoprazan triple-drug blister packs, daily doses are combined in one "sheet" and seven sheets are prescribed for 1 week (Fig. 1).

Fig. 1 Vonoprazan triple-drug blister pack (VONOSAP®): Contains vonoprazan, clarithromycin, and amoxicillin (from left to right)

Additionally, medicines to be taken in the morning and evening are color-coded in the center. In a retrospective study looking at lansoprazole triple therapy, the eradication success rate was higher in the triple-drug blister pack group than in the separate-tablets group [23]. Conversely, the eradication success rate was the same in another retrospective study that examined vonoprazan triple therapy [24]. Moreover, there was no significant difference between the two groups in RCTs [25, 26]. It is possible that the RCTs were affected by the Hawthorne effect because not only the blister pack group but also the separate-tablets group had good compliance; therefore, the full impact of the combination blister pack on the success rate of clarithromycin triple therapy remains unclear. It has been hypothesized that the launch of the vonoprazan triple-drug blister pack in June 2016 increased the proportion of vonoprazan and combination blister pack use, which may have improved *H. pylori* eradication success rates in Japan as a whole. However, no studies have evaluated whether launch of the vonoprazan triple-drug blister pack has increased the *H. pylori* eradication success rate. The present study aimed to assess the immediate change in eradication success rate of clarithromycin triple therapy before and after launch of the vonoprazan triple-drug blister pack.

METHODS

Study Design

As a primary outcome, an interrupted time series (ITS) analysis was conducted to examine changes in clarithromycin triple therapy success rate. For secondary endpoints, the proportion of vonoprazan use and proportion of triple-drug blister pack use were investigated. ITS analysis is considered to be within the highest tier of hierarchy in terms of quasi-experimental design and is useful in assessing the impact of interventions/reforms compared with a simple pre–post design [27]. One of the strengths of ITS analysis is that it is generally unaffected by typical confounding variables, which remain fairly constant, including clarithromycin-resistant *H. pylori* or baseline drug compliance, as these only change relatively slowly over time and are normally taken into account when modelling the underlying long-term trend [28]. ITS analysis is considered to be particularly effective for evaluation of population-level interventions, such as in cases where no control or comparison group is available [28]. We assessed whether the point at which the vonoprazan triple-drug blister pack was launched (June 2016) was associated with immediate increases (a change in the intercept) at the time of interruption or a change in the trajectory over time (the slope). Other triple-drug blister packs containing PPIs such as lansoprazole or rabeprazole were available by 2014 and vonoprazan itself was introduced in February 2015. Therefore, the intervention of this study is

considered to be the launch of the vonoprazan triple-drug blister pack only.

Patients

We utilized data from a large health insurance claims database provided by JMDC Inc. (Tokyo, Japan). This database contains hospital outpatient, hospital inpatient, and pharmacy data from more than 90 employee-based health insurance societies; it includes data from approximately 7,300,000 insured Japanese individuals (representing around 6% of the entire population of Japan). For each person, the JMDC database includes an enciphered personal identifier, family identifier, age, sex, diagnoses, medical services, and drugs prescribed. Enciphered personal identifiers were used to link claims data from different medical institutions and pharmacies. The investigators could only access anonymized information from the JMDC database; therefore, in accordance with the Japanese Ethical Guidelines, institutional ethics approval and informed consent were not required.

In this study, patients who had records for prescription of first-line clarithromycin triple therapy (clarithromycin, amoxicillin, and a PPI or vonoprazan) between June 1, 2015 and July 31, 2017 were included. Vonoprazan was launched before this period on February 26, 2015, and the vonoprazan triple-drug blister pack was launched on June 7, 2016. Patients who had records for prescriptions of second-line therapy (metronidazole, amoxicillin, and a PPI) before receiving first-line therapy were excluded.

Success Rate of Clarithromycin Triple Therapy Against *H. pylori* (Primary Endpoint)

The only first-line *H. pylori* eradication therapy covered by insurance in Japan is a combination of clarithromycin, amoxicillin, and a PPI or vonoprazan. If patients fail first-line clarithromycin triple therapy then a combination of metronidazole, amoxicillin, and a PPI or vonoprazan is provided as second-line eradication therapy and this is the only regimen covered by insurance. Because *H. pylori* infection test results are not available in the database, a previously used definition was applied [19, 29]. Specifically, failure of clarithromycin triple therapy was defined as the prescription of second-line therapy after completion of first-line clarithromycin triple therapy. Similarly, the repeat administration of first-line clarithromycin triple therapy was defined as failure of clarithromycin triple therapy. Successful clarithromycin triple therapy was defined as the prescription of first-line clarithromycin triple therapy that did not require the repeat of first-line therapy or the receipt of a second line of treatment. The monthly success rate was based on receipt of first-line therapy each month and success or failure was determined by receipt or not of second-line therapy after that.

Proportion of Vonoprazan Use to Overall PPIs and P-CAB Use for *H. pylori* Eradication (Secondary Endpoint)

The use of vonoprazan was defined as the receipt of a vonoprazan first-line triple-therapy regimen comprising clarithromycin, amoxicillin, and vonoprazan, or the receipt of vonoprazan triple-drug blister pack. Data used for the denominator were those with recorded prescriptions for any first-line clarithromycin triple therapy. This was assessed because the launch of the vonoprazan triple-drug blister pack may improve *H. pylori* eradication success through the increase in overall vonoprazan use regardless of separate tablets or combination blister pack.

Proportion of Combination Blister Pack Use for *H. pylori* Eradication (Secondary Endpoint)

The use of combination blister packs was defined as the receipt of any combination blister pack containing lansoprazole, rabeprazole, or vonoprazan. Data used for the denominator were those with recorded prescriptions for any first-line clarithromycin triple therapy. This was assessed because the launch of the vonoprazan

triple-drug blister pack may also have improved *H. pylori* eradication success rates through the increase in combination blister pack use.

Comorbidities

Comorbidities that may lead to necessitate *H. pylori* eradication were defined on the basis of the World Health Organization International Classification of Diseases, 10th Revision, or Japanese Standard Disease Names (JSDN): peptic ulcer (K25–K28), gastritis (K29.3–K29.5, *Helicobacter pylori* gastritis [JSDN], intestinal metaplasia [JSDN]), and gastric MALT lymphoma (JSDN) [30, 31]. These were compared between prelaunch and post-launch periods.

Statistical Analysis

Patient characteristics were expressed as mean (standard deviation [SD]). For ITS, the time series was generated from monthly success rates of clarithromycin triple therapy and proportion of vonoprazan use and proportion of combination blister pack use compared with those who had prescription records for first-line clarithromycin triple therapy. This led to the generation of 25 months of data (observations) in our time series, aligning with the number of months between June 2015 and June 2017. We considered a lag period of 1 month before the true influence of the vonoprazan triple-drug blister pack could be observed on the outcomes because some hospitals did not adopt the combination pack (VONOSAP®) in the launch month; therefore, data in June 2016 were excluded. Monthly success rate and proportion of vonoprazan and of combination blister pack use were then utilized to compare changes between the pre- and post-launch periods of vonoprazan triple-drug blister pack using ITS analysis. The following equation was used for the regression: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \varepsilon_t$, where Y_t is the aggregated proportions measured at month t; T_t is the time since the start of observation (in months); X_t is a dummy (indicator) variable representing the launch of vonoprazan triple-drug blister pack (prelaunch periods = 0, post-launch periods = 1); and, $X_t T_t$ is an interaction term. The models were parameterized to test for both a one-time change immediately at the time of implementation (intercept; β_2) and the difference in the pre- and post-launch trends (slope; β_3). The Durbin–Watson statistic was used to examine for the presence of autocorrelation among serial observations, and the model was corrected for autocorrelation if required [32]. The ITS analysis was conducted in accordance with the Cochrane Effective Practice and Organization of Care Review Group recommendations [33].

We conducted two sensitivity analyses to confirm the robustness of the analysis. First, to determine the effect on inferences instead of a lag period of 1 month, models excluded 3 months between June 2016 and August 2016 to account for possible gradual launch effects on practice. Second, to exclude patients who may have been lost to treatment follow-up, we restricted patients to those who had been tested for *H. pylori* infection at any time after completion of first-line clarithromycin triple therapy of the primary analysis. Procedures or drug codes for the following were considered tests for the confirmation of *H. pylori* eradication: rapid urease test, microbial culture, urea breath test, antibody measurement, and stool antigen test.

A P value less than 0.05 was considered statistically significant. SAS 9.4 (SAS Institute, Cary, USA) and R 3.5.1 (The R Foundation, Vienna, Austria) were used to perform the statistical analyses. The analyses in this study were conducted with no missing data.

RESULTS

Patient Characteristics

A total of 36,570 patients received first-line clarithromycin triple therapy during the prelaunch period and 35,721 patients received the same therapy during the post-launch period. Table 1 shows characteristics of the study patients. Mean age of patients was 51.8 (SD 10.3) and 50.9 (SD 10.3) years, respectively; number of women was 15,677 (42.9%) and 14,748 (41.3%) during prelaunch and post-launch periods, respectively.

Table 1 Patient characteristics

	Prelaunch period[a] (*n* = 36,570)	Post-launch period[b] (*n* = 35,721)
Age, years	51.8 ± 10.3	50.9 ± 10.3
Men/women, *n*	20,893/15,677	20,973/14,748
Peptic ulcer, *n* (%)	11,579 (31.7)	11,135 (31.2)
Gastritis, *n* (%)	31,424 (85.9)	31,224 (87.4)
Gastric MALT lymphoma, *n* (%)	17 (0.05)	19 (0.05)

Continuous data are expressed as mean ± standard deviation

MALT mucosa-associated lymphoid tissue

[a] Prelaunch period was June 2015 to May 2016

[b] Post-launch period was July 2016 to June 2017

Success Rate of Clarithromycin Triple Therapy (Primary Endpoint)

The success rate of first-line clarithromycin triple therapy was 83.1% (2574/3096) in June 2015, increasing to 92.0% (3088/3355) by June 2017. In June 2016, an immediate change in success rate was observed. The ITS analysis showed a 2.44% (95% CI 1.36–3.52; $P < 0.0001$) increase in clarithromycin triple-therapy success rate from May 2016 to July 2016 (Fig. 2a; Table 2). Slope of regression lines did not show a significant difference between the two periods (− 0.08%; 95% CI − 0.22 to 0.07; $P = 0.30$). The Durbin–Watson test was not significant at certain lags apart from up to 12 months, suggesting nonsignificant autocorrelation.

Proportion of Vonoprazan Use Relative to Overall PPIs and P-CAB Use for *H. pylori* Eradication (Secondary Endpoint)

The proportion of vonoprazan use relative to overall PPI and P-CAB use for *H. pylori* eradication was 39.9% (1235/3096) in June 2015, increasing to 84.5% (2836/3355) by June 2017. In June 2016, an immediate change was observed. The ITS analysis showed a 12.7%

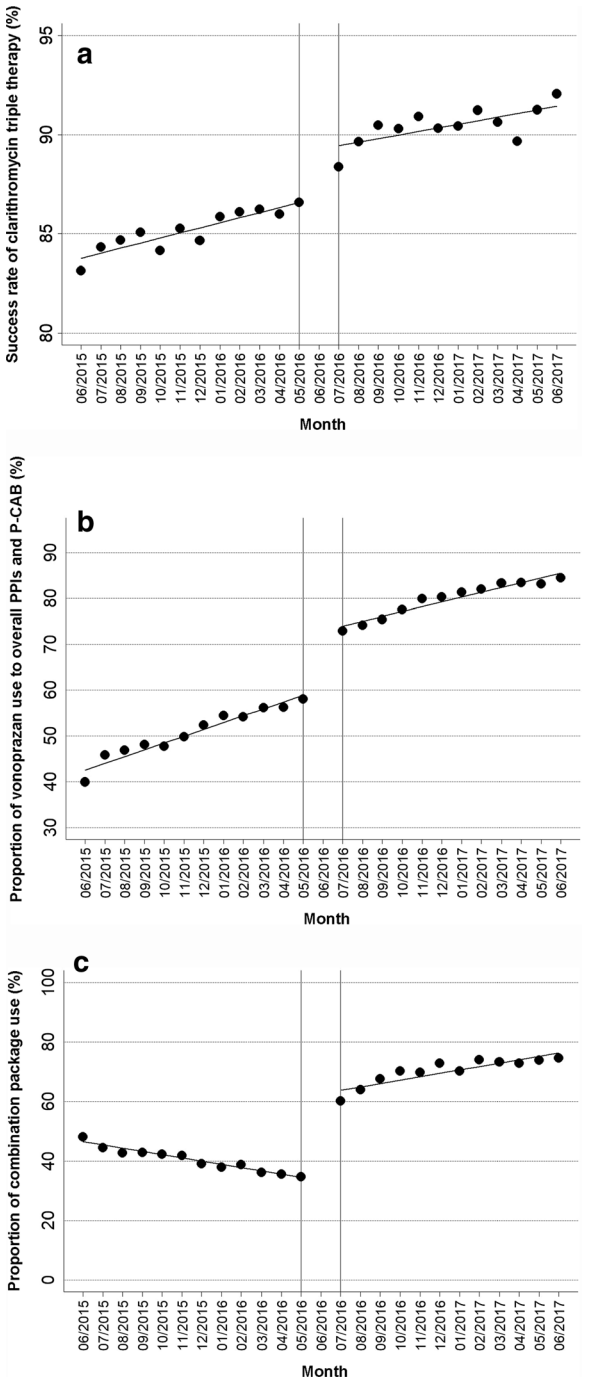

Fig. 2 Outcomes before and after launch of vonoprazan triple-drug blister pack in June 2016. **a** Success rate of clarithromycin triple therapy. **b** Proportion of vonoprazan use to overall PPIs and P-CAB use. **c** Proportion of triple-drug blister pack use. *P-CAB* potassium-competitive acid blockers, *PPI* proton-pump inhibitor

Table 2 Interrupted time series analysis before and after launch of vonoprazan combination blister pack in June 2016

Outcome	Just before launch	Just after launch	Change associated with launch of vonoprazan combination package			
	Level at the last month before launch, %[a]	Level at the first month after launch, %[b]	Immediate change[c] (95% CI)	*P* value	Change in slope (95% CI)	*P* value
Success rate of clarithromycin triple therapy	86.6	88.4	2.44 (1.36 to 3.52)	< 0.0001	− 0.08 (− 0.22 to 0.07)	0.30
Proportion of vonoprazan use to overall PPI and P-CAB use	58.0	73.0	12.7 (10.0 to 15.3)	< 0.0001	− 0.45 (− 0.82 to − 0.08)	0.03
Proportion of triple-drug blister pack use	34.7	60.1	29.2 (25.4 to 32.9)	< 0.0001	2.24 (1.71 to 2.76)	< 0.0001

CI confidence interval, *P-CAB* potassium-competitive acid blockers, *PPI* proton-pump inhibitor
[a] The last month before launch was May 2016
[b] The first month after launch was July 2016
[c] Immediate change represents the intercept, an increase or decrease from May 2016 to July 2016 that is distinct from ongoing trends

(95% CI 10.0–15.3; $P < 0.0001$) increase in vonoprazan use proportional to overall PPI and P-CAB use from May 2016 to July 2016 (Fig. 2b; Table 2). Slope of regression lines decreased between the two periods (− 0.45%; 95% CI − 0.82 to − 0.08; $P = 0.03$). We corrected a first-order autocorrelation, because the Durbin–Watson test was significant at lag apart from a 1-month period.

Proportion of Combination Blister Pack Use for *H. pylori* Eradication (Secondary Endpoint)

The proportion of combination blister pack use for *H. pylori* eradication was 48.2% (1491/3096) in June 2015, increasing to 74.5% (2501/3355) by June 2017. In June 2016, the immediate change was observed. The ITS analysis showed a 29.2% (95% CI 25.4–32.9; $P < 0.0001$) increase in combination blister pack use from May 2016 to July 2016 (Fig. 2c; Table 2). Slope of regression lines also increased between the two periods (2.24%; 95% CI 1.71–2.76; $P < 0.0001$). We corrected a first-order autocorrelation, because the Durbin–Watson test was significant at lag apart from a 1-month period.

Sensitivity Analysis

First, instead of a lag period of 1 month, a model was conducted in which a lag of 3 months from June 2016 to August 2016 was excluded. Inferences were unchanged relative to the main models. The success rate of clarithromycin triple therapy increased by 2.86% (95% CI 1.81–3.91; $P < 0.0001$) from May 2016 to September 2016. Slope of regression lines decreased between the two periods (− 0.16%; 95% CI − 0.28 to − 0.03; $P = 0.02$). Likewise, the proportion of vonoprazan use increased by 13.6% (95% CI 10.6–16.5; $P < 0.0001$) and slope of regression lines decreased between the two periods (− 0.73%; 95% CI − 1.08 to − 0.38; $P < 0.0001$). Proportion of blister pack use increased by 37.1% (95% CI 34.9–39.3; $P < 0.0001$) and slope of regression lines also increased between the two periods (1.77%; 95%

CI 1.50–2.04; $P < 0.0001$). Second, we restricted patients to those who were tested for *H. pylori* infection after receiving first-line clarithromycin triple therapy of the primary analysis. The success rate of clarithromycin triple therapy increased by 3.01% (95% CI 1.86–4.17; $P < 0.0001$) from May 2016 to September 2016. Slope of regression lines did not show a significant difference between the two periods (− 0.11%; 95% CI − 0.26 to 0.05; $P = 0.17$).

DISCUSSION

This is the first study to show an actual change in success rate of clarithromycin triple therapy after vonoprazan triple-drug blister pack launch, by analysis of a large health claims database at an individual level. As hypothesized, the launch of the vonoprazan triple-drug blister pack for *H. pylori* eradication increased the success rate of clarithromycin triple therapy and the proportion of vonoprazan and of combination blister pack use. Moreover, the robust association was confirmed by two sensitivity analyses (one with adjusted lag periods of 3 months, and another in which patients were restricted to those who were tested for *H. pylori* infection after first-line clarithromycin triple therapy). In contrast, the trends (slope) were not markedly different between pre- and post-launch, and were actually almost flat. This may be because the clarithromycin success rate and the proportion of vonoprazan use reached the practical upper limit.

The results of the current study are consistent with those of previous studies. In the phase 3 clinical trial, the eradication success rate of clarithromycin triple therapy with vonoprazan was 92.6% and with lansoprazole, a PPI, 75.9%; noninferiority was confirmed in the primary analysis and superiority was confirmed in an additional analysis [21]. In our study, an immediate increase of 12.7% was observed in the proportion of vonoprazan use, which may have contributed to the immediate increase in the eradication success rate. Reducing the burden of complex prescribing with clarithromycin triple therapy can mean easier and more accurate administration of medicine, which may be preferable for patients and doctors.

Additionally, the eradication success rate of a lansoprazole triple-drug blister pack group was shown to be higher than that of a separate-tablets group in a retrospective study [24]. Although two RCTs demonstrated that the difference in success rate between the groups was not significant, the Hawthorne effect may have impacted the RCTs because both groups had good drug compliance [25, 26]. In our study, the immediate increase in the proportion of combination blister pack use was 29.2%, which may have led to the immediate increase in the eradication success rate with the increase in the proportion of vonoprazan use. Further studies are needed to evaluate whether drug compliance increases the success rate of *H. pylori* eradication in the real world.

The present study has two limitations. First, because the results of *H. pylori* infection tests were not available in the database, success of clarithromycin triple therapy was defined by lack of second-line therapy after having received first-line clarithromycin triple therapy. This definition may be prone to misclassification bias because those who had failed the first time but decided not to receive second-line therapy were regarded as successfully treated. Nevertheless, the clarithromycin triple therapy success rate of the current study (87.8%) was consistent with that of previous studies: 74.8–91.4% [34–38]. Therefore, we propose that the eradication success rate calculated in this study is comparable to the true eradication success rate. Secondly, we cannot rule out the possibility of bias due to concurrent interventions. For instance, in September 2016, Japanese clinical guidelines for *H. pylori* diagnosis were released, which may have also contributed to increased vonoprazan use. However, this influence is proposed to be limited because the increase was already observed before the guidelines were released.

CONCLUSION

This is the first study to demonstrate an immediate increase in clarithromycin triple-therapy

success rate, with a greater proportion of vonoprazan use and a greater proportion of combination blister pack use after the vonoprazan triple-drug blister pack was launched. These findings suggest that introducing easily administered formulations may be effective in changing prescribing practice and subsequent patient outcomes.

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Compliance with Ethics Guidelines. The study was conducted according to the Declaration of Helsinki and the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices. It was carried out retrospectively using a database of anonymized data, following Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labor, and Welfare [39]. The investigators could only access anonymized information from JMDC database; therefore, in accordance with the Japanese Ethical Guidelines mentioned above, institutional ethics approval and informed consent were not required.

Data Availability. The data that support the findings of this study are available from JMDC Inc. but were used under license for the current study; therefore, restrictions apply, and the data are not publicly available. For inquiries about access to the data set used in this study, please contact JMDC (https://www.jmdc.co.jp).

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