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Health Care Cost Analysis of PPI or P-CAB-First Treatment in Patients With Gastroesophageal Reflux Disease

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Goals: The aim was to examine actual health care cost in patients with gastroesophageal reflux disease (GERD) who were initiated on proton pump inhibitor (PPI) or potassium-competitive acid blocker (P-CAB) as first-line therapy in Japanese real-world clinical settings.

Background: To date, cost-utility evaluation of acid-suppressants treatment in Japan has only been conducted by model analysis.

Study: A cost utilization analysis was performed using a Japanese nationwide hospital-based claim database by extracting patients with GERD initiated on either PPI or P-CAB (242,102 pairs) and esomeprazole (EPZ) or P-CAB (241,825 pairs). Health care costs were compared in each comparison cohort with propensity-score matched pairs. The switching rates of initial acid-suppressants were also examined.

Results: Baseline characteristics were well-balanced after matching. The 3-year mean cumulative GERD-related and hospitalization costs per patient were ¥142,620 and ¥122,444 in PPI-first and P-CAB-first treatment groups, and ¥105,263 and ¥121,958 in EPZ-first and P-CAB-first treatment groups, respectively. Most hospitalization costs were non-GERD related in all the groups. The switching rates of PPI to P-CAB and P-CAB to PPI in 12 months were 7.5% and 20.2%, respectively.

Conclusions: In this propensity-score matched analysis, health care cost was higher in patients with GERD initiated on PPI than in those initiated on P-CAB mainly owing to non-GERD-related hospitalization cost, whereas it was lower in those initiated on EPZ than in those initiated on P-CAB. When considering health care costs except hospitalization costs, PPI-first treatment was less expensive than P-CAB-first treatment. Low switching rate from PPI to P-CAB in the real-world practice may partially explain the discrepancy.

Key Words: proton pump inhibitor, potassium-competitive acid blocker, health care cost

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Gastroesophageal reflux disease (GERD) is one of the most common digestive diseases in which acid-containing gastric contents reflux from the stomach to esophagus and leads uncomfortable symptoms, such as heartburn. The control of secretion of gastric acid is the main strategy for the treatment of this disease. The guideline for GERD recommends the use of proton pump inhibitor (PPI) for the treatment of GERD based on its definite effect on suppressing acid secretion.[1] Recently, a new acid suppressant called potassium-competitive acid blocker (P-CAB)[2,3] has been approved and widely used in the treatment of GERD in Japan. The guideline has recently been revised and P-CAB is also recommended for reflux esophagitis (RE).

Previously, 2 studies have conducted by utilizing Markov simulation model to analyze cost-effectiveness of P-CAB-based and PPI-based treatments[4,5] in Japan and reported better cost-effectiveness of P-CAB-based treatment than PPI-based. However, these results were simulated based on an assumption of healing and relapse effects in patients with relatively severe GERD while 90% of patients with actual GERD were reported to be mild–to-moderate in Japan.[6] Because it is practically difficult to incorporate all the factors affecting health care costs into cost-effectiveness models, it is important to confirm the consistency of the model-based cost prediction with actual cost utilization in the real-world when necessary data become available.

The aim of this study is to develop holistic view of real-world GERD management by evaluating the actual health care costs associated with contemporary GERD treatment using PPIs and P-CAB in Japan. Our findings based on one of the largest nationwide database will provide practical insights into treatment strategies and decision making toward value-based GERD treatment.

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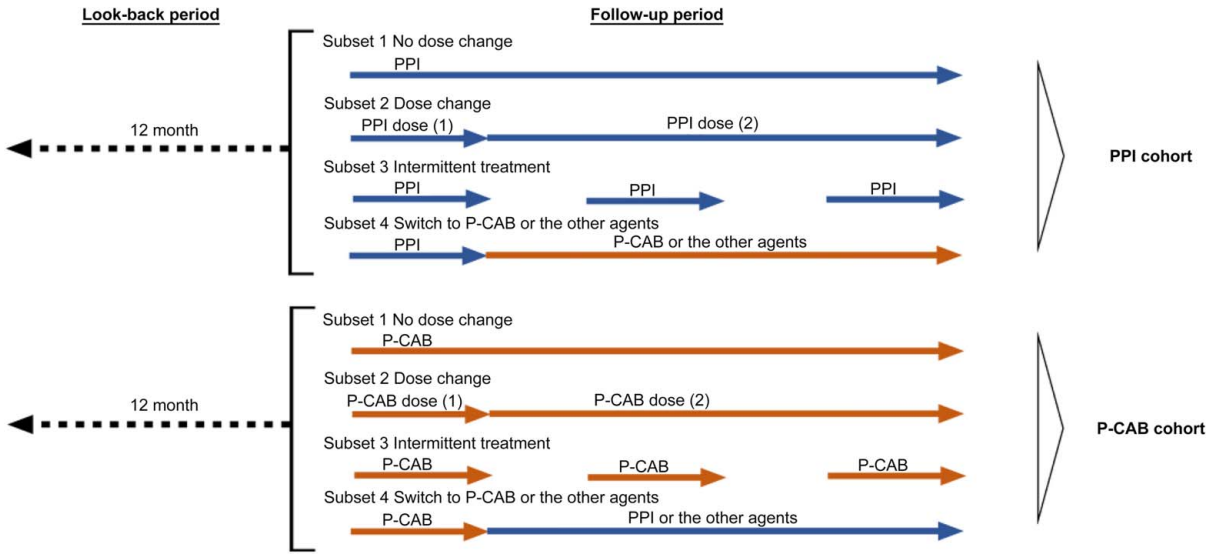

FIGURE 1. The scheme of patient look-back and follow-up. Each of subset (subsets 1 to 4) includes patients who discontinued receiving prescription during follow-up period. PPI indicates proton pump inhibitor; P-CAB, potassium-competitive acid blocker.

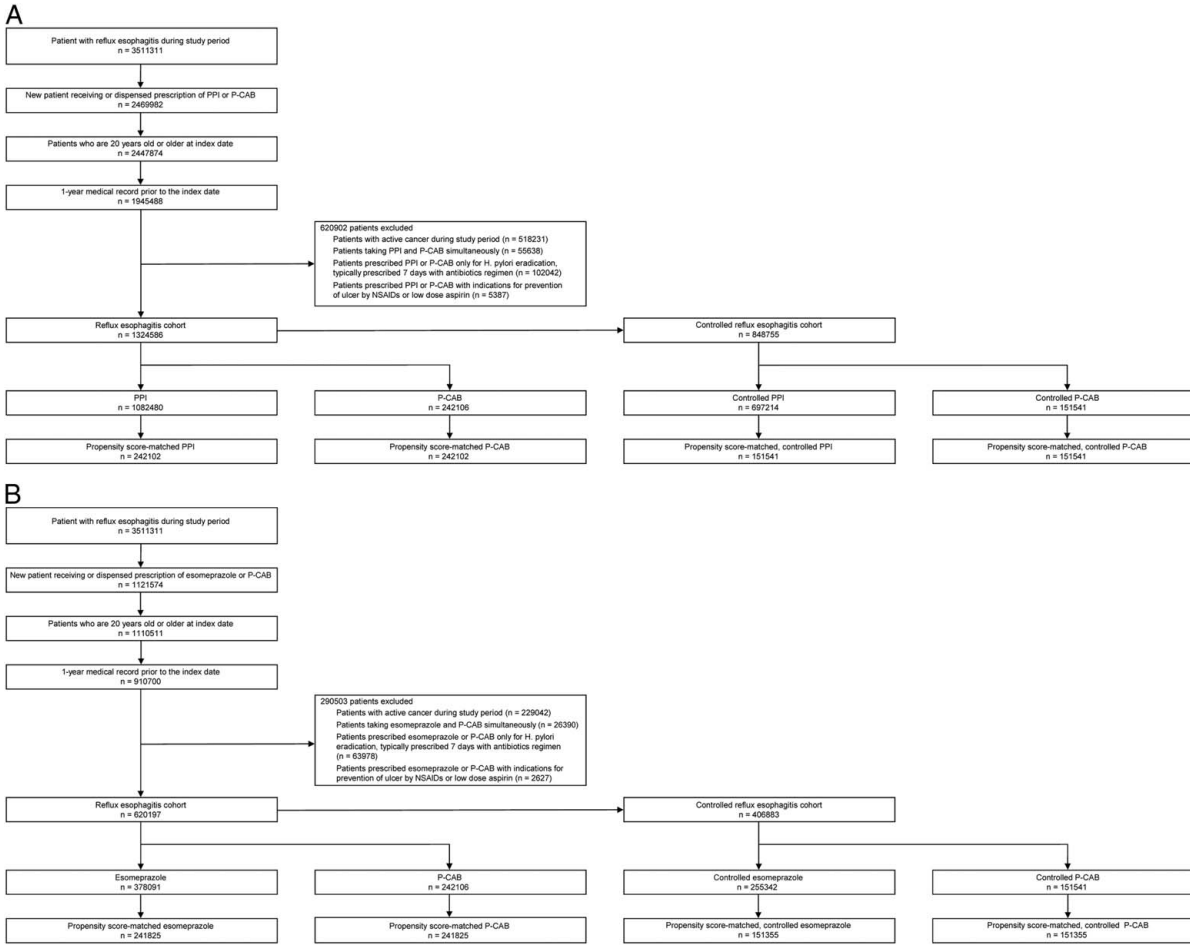

FIGURE 2. A, Disposition of patients with reflux esophagitis [proton pump inhibitor (PPI) vs. potassium-competitive acid blocker (P-CAB)]. B, Disposition of patients with reflux esophagitis [esomeprazole (EPZ) vs. P-CAB].

TABLE 1. Baseline Demographic and Clinical Characteristics (Overall Population, Patients With Reflux Esophagitis)

	Unmatched Cohort			Matched Cohort			Unmatched Cohort			Matched Cohort		
	PPI (N = 1,082,480)	P-CAB (N = 242,106)	SD (%)	PPI (N = 242,102)	P-CAB (N = 242,102)	SD (%)	Esomeprazole (N = 378,091)	P-CAB (N = 242,106)	SD (%)	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	SD (%)
Age, years												
Mean (SD)	65.2 (17.9)	63.1 (17.5)	11.8	64.2 (17.8)	63.1 (17.5)	6.6	61.9 (17.9)	63.1 (17.5)	−6.4	62.6 (17.7)	63.0 (17.5)	−2.3
Gender												
Male	539,889 (49.9)	125,138 (51.7)	−3.6	116,599 (48.2)	125,137 (51.7)	−7.1	188,563 (49.9)	125,138 (51.7)	−3.6	107,967 (44.6)	124,918 (51.7)	−14.1
Female	542,591 (50.1)	116,968 (48.3)		125,503 (51.8)	116,965 (48.3)		189,528 (50.1)	116,968 (48.3)		133,858 (55.4)	116,907 (48.3)	
Endoscopic examination												
Mean (SD)	0.1 (0.3)	0.1 (0.3)	−3.0	0.1 (0.3)	0.1 (0.3)	−0.6	0.1 (0.3)	0.1 (0.3)	1.6	0.1 (0.3)	0.1 (0.3)	1.9
Medical history												
Barrett's esophagus	2678 (0.2)	832 (0.3)	−1.8	799 (0.3)	831 (0.3)	−0.2	937 (0.2)	832 (0.3)	−1.8	771 (0.3)	828 (0.3)	−0.4
Hiatus hernia	11147 (1.0)	3012 (1.2)	−2.0	3555 (1.5)	3012 (1.2)	1.9	4138 (1.1)	3012 (1.2)	−1.4	2970 (1.2)	3008 (1.2)	−0.1
Chronic pharyngitis	75,396 (7.0)	17,368 (7.2)	−0.8	23,036 (9.5)	17,368 (7.2)	8.5	31,335 (8.3)	17,368 (7.2)	4.2	20,750 (8.6)	17,366 (7.2)	5.2
Sleep disorders	137,128 (12.7)	26,825 (11.1)	4.9	32,910 (13.6)	26,824 (11.1)	7.6	43,371 (11.5)	26,825 (11.1)	1.2	29,132 (12.0)	26,785 (11.1)	3.0
Scleroderma	2761 (0.3)	645 (0.3)	−0.2	847 (0.3)	645 (0.3)	1.5	1038 (0.3)	645 (0.3)	0.2	654 (0.3)	645 (0.3)	0.1
Gastric ulcer	154,145 (14.2)	36,789 (15.2)	−2.7	36,787 (15.2)	36,787 (15.2)	0.0	53,854 (14.2)	36,789 (15.2)	−2.7	36,440 (15.1)	36,653 (15.2)	−0.2
Duodenal ulcer	13,095 (1.2)	3380 (1.4)	−1.6	4044 (1.7)	3380 (1.4)	2.2	3528 (0.9)	3380 (1.4)	−4.3	2989 (1.2)	3326 (1.4)	−1.2
Anastomotic ulcer	201 (0.0)	39 (0.0)	0.2	75 (0.0)	39 (0.0)	1.0	40 (0.0)	39 (0.0)	−0.5	37 (0.0)	39 (0.0)	−0.1
Gastritis and duodenitis	201,888 (18.7)	52,233 (21.6)	−7.3	51,365 (21.2)	52,230 (21.6)	−0.9	83,602 (22.1)	52,233 (21.6)	1.3	56,564 (23.4)	52,196 (21.6)	4.3
Upper gastrointestinal bleeding, Hematemesis, Bloody stool	23,517 (2.2)	3520 (1.5)	5.4	4348 (1.8)	3518 (1.5)	2.7	4644 (1.2)	3520 (1.5)	−2.0	3374 (1.4)	3497 (1.4)	−0.4
Helicobacter pylori infection	16,127 (1.5)	5148 (2.1)	−4.8	4349 (1.8)	5146 (2.1)	−2.4	7161 (1.9)	5148 (2.1)	−1.7	5142 (2.1)	5139 (2.1)	0.0
Crohn's disease	2167 (0.2)	351 (0.1)	1.3	445 (0.2)	351 (0.1)	1.0	900 (0.2)	351 (0.1)	2.1	468 (0.2)	351 (0.1)	1.2
Ulcerative colitis	8559 (0.8)	1453 (0.6)	2.3	1955 (0.8)	1453 (0.6)	2.5	3834 (1.0)	1453 (0.6)	4.6	1885 (0.8)	1453 (0.6)	2.2
Myocardial infarction	38,593 (3.6)	11,185 (4.6)	−5.3	8151 (3.4)	11,185 (4.6)	−6.4	12,042 (3.2)	11,185 (4.6)	−7.4	10,038 (4.2)	11,078 (4.6)	−2.1
Stroke	58,791 (5.4)	11,070 (4.6)	3.9	12,340 (5.1)	11,070 (4.6)	2.4	13,645 (3.6)	11,070 (4.6)	−4.9	10,024 (4.1)	10,941 (4.5)	−1.9
Obesity	4242 (0.4)	912 (0.4)	0.2	1127 (0.5)	912 (0.4)	1.4	1370 (0.4)	912 (0.4)	−0.2	922 (0.4)	912 (0.4)	0.1
Peripheral vascular disease	3291 (0.3)	615 (0.3)	0.9	840 (0.3)	615 (0.3)	1.7	915 (0.2)	615 (0.3)	−0.2	616 (0.3)	613 (0.3)	0.0
Cerebrovascular disease	9398 (0.9)	2440 (1.0)	−1.4	2456 (1.0)	2440 (1.0)	0.1	2604 (0.7)	2440 (1.0)	−3.5	2147 (0.9)	2421 (1.0)	−1.2
Dementia	57,209 (5.3)	8319 (3.4)	9.1	9376 (3.9)	8318 (3.4)	2.3	11,973 (3.2)	8319 (3.4)	−1.5	8236 (3.4)	8307 (3.4)	−0.2
Asthma	71,132 (6.6)	13,616 (5.6)	4.0	15,820 (6.5)	13,616 (5.6)	3.8	26,880 (7.1)	13,616 (5.6)	6.1	15,916 (6.6)	13,616 (5.6)	4.0
Chronic pulmonary disease	115,245 (10.6)	21,736 (9.0)	5.6	25,320 (10.5)	21,735 (9.0)	5.0	41,669 (11.0)	21,736 (9.0)	6.8	25,586 (10.6)	21,735 (9.0)	5.4
Collagen disease	4735 (0.4)	958 (0.4)	0.6	1094 (0.5)	958 (0.4)	0.9	1816 (0.5)	958 (0.4)	1.3	1125 (0.5)	957 (0.4)	1.1
Liver disease	59,729 (5.5)	12,385 (5.1)	1.8	15,708 (6.5)	12,385 (5.1)	5.9	22,354 (5.9)	12,385 (5.1)	3.5	14,565 (6.0)	12,382 (5.1)	3.9
Hemiplegia	22,363 (2.1)	4081 (1.7)	2.8	5149 (2.1)	4081 (1.7)	3.2	5380 (1.4)	4081 (1.7)	−2.1	3772 (1.6)	3971 (1.6)	−0.7
Any tumor	194 (0.0)	0	1.9	0	0	—	66 (0.0)	0	1.9	0	0	—
Leukemia	6 (0.0)	0	0.3	0	0	—	1 (0.0)	0	0.2	0	0	—
Metastatic solid tumor	12 (0.0)	0	0.5	0	0	—	4 (0.0)	0	0.5	0	0	—
AIDS	585 (0.1)	96 (0.0)	0.7	134 (0.1)	96 (0.0)	0.7	196 (0.1)	96 (0.0)	0.6	117 (0.0)	96 (0.0)	0.4
AF or atrial flutter	111,369 (10.3)	23,544 (9.7)	1.9	23,365 (9.7)	23,544 (9.7)	−0.2	34,765 (9.2)	23,544 (9.7)	−1.8	24,136 (10.0)	23,537 (9.7)	0.8
Valvular heart disease	56,497 (5.2)	10,916 (4.5)	3.3	14,366 (5.9)	10,915 (4.5)	6.4	15,764 (4.2)	10,916 (4.5)	−1.7	10,596 (4.4)	10,908 (4.5)	−0.6
Esophageal surgery/ endoscopic treatment/ examination	16,612 (1.5)	3244 (1.3)	1.6	3506 (1.4)	3242 (1.3)	0.9	5613 (1.5)	3244 (1.3)	1.2	3481 (1.4)	3243 (1.3)	0.8
Gastroduodenal surgery/ endoscopic treatment/ examination	80,760 (7.5)	18,903 (7.8)	−1.3	19,106 (7.9)	18,900 (7.8)	0.3	31,622 (8.4)	18,903 (7.8)	2.0	20,415 (8.4)	18,897 (7.8)	2.3
History of hospitalization	289,353 (26.7)	52,115 (21.5)	12.2	58,164 (24.0)	52,113 (21.5)	6.0	84,139 (22.3)	52,115 (21.5)	1.8	54,233 (22.4)	52,106 (21.5)	2.1
Emergency visit	161,796 (14.9)	28,683 (11.8)	9.1	31,130 (12.9)	28,682 (11.8)	3.1	41,841 (11.1)	28,683 (11.8)	−2.5	27,338 (11.3)	28,681 (11.9)	−1.7
ICU admission	42,812 (4.0)	9739 (4.0)	−0.3	9514 (3.9)	9739 (4.0)	−0.5	10,489 (2.8)	9739 (4.0)	−6.9	8521 (3.5)	9736 (4.0)	−2.6
Pretreatment												
H2-RA	90,575 (8.4)	19,627 (8.1)	0.9	20,380 (8.4)	19,626 (8.1)	1.1	29,906 (7.9)	19,627 (8.1)	−0.7	19,602 (8.1)	19,620 (8.1)	0.0
M-RA	47 (0.0)	8 (0.0)	0.2	7 (0.0)	8 (0.0)	−0.1	12 (0.0)	8 (0.0)	0.0	8 (0.0)	8 (0.0)	0.0

Antacid	96,772 (8.9)	21,288 (8.8)	0.5	22,070 (9.1)	21,285 (8.8)	1.1	35,487 (9.4)	21,288 (8.8)	2.1	22,789 (9.4)	21,283 (8.8)	2.2
Esophageal/gastric mucosa protectants	120,640 (11.1)	26,574 (11.0)	0.5	28,790 (11.9)	26,573 (11.0)	2.9	44,502 (11.8)	26,574 (11.0)	2.5	29,121 (12.0)	26,570 (11.0)	3.3
Prokinetic agents	84,475 (7.8)	19,280 (8.0)	−0.6	20,033 (8.3)	19,280 (8.0)	1.1	29,830 (7.9)	19,280 (8.0)	−0.3	19,460 (8.0)	19,274 (8.0)	0.3
Antiplatelets	127,215 (11.8)	28,564 (11.8)	−0.1	28,946 (12.0)	28,564 (11.8)	0.5	38,450 (10.2)	28,564 (11.8)	−5.2	25,834 (10.7)	28,558 (11.8)	−3.6
Anticoagulants	60,512 (5.6)	14,043 (5.8)	−0.9	13,850 (5.7)	14,043 (5.8)	−0.3	19,872 (5.3)	14,043 (5.8)	−2.4	12,820 (5.3)	14,036 (5.8)	−2.2
NSAIDs/Aspirin	222,830 (20.6)	46,974 (19.4)	3.0	51,301 (21.2)	46,973 (19.4)	4.4	75,813 (20.1)	46,974 (19.4)	1.6	49,903 (20.6)	46,966 (19.4)	3.0
Total health care cost (in 3 mo before the index date)												
n	718,303	155,101	4.4	155,101	155,099	0.2	247,386	155,101	−3.8	155,098	155,097	−1.5
Mean (SD)	366,989.08 (680,415.90)	336,918.72 (684,552.17)		338,271.13 (656,086.99)	336,914.46 (684,554.52)		312,101.27 (618,848.62)	336,918.72 (684,552.17)		326,995.05 (643,019.50)	336,894.29 (684,506.67)	
Total health care cost (in 12 mo before the index date)												
n	779,077	170,672	3.8	189,977	170,668	−3.9	272,241	170,672	−2.9	177,508	170,640	−2.7
Mean (SD)	483,307.72 (937,494.58)	447,797.86 (929,057.53)		412,608.99 (854,744.63)	447,798.30 (929,066.76)		422,056.47 (860,548.76)	447,797.86 (929,057.53)		423,133.13 (878,055.96)	447,799.99 (929,048.15)	

Values are number (percent) or mean (standard deviation).
ICU indicates intensive care unit; NSAIDs, non-steroidal anti-inflammatory drug; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

MATERIALS AND METHODS

Study Design

This study was a retrospective, observational, cohort study using the Medical Insurance Claim Database in the clinical practice in Japan, aiming to describe actual health care costs in Japanese patients with GERD who were treated with PPIs or P-CAB.

The study period consisted of 2 observation periods: the look-back period (at least 12 mo) and follow-up period. The index date was set on the date of initial prescription for medications as treatment of GERD, with confirming no previous treatment history of GERD during the look-back period. Therefore, the treatment started on the index date was the first-line treatment of GERD for that patient.

Database Selection

In this study, we used the data provided by Medical Data Vision Co., Ltd., which is one of the largest hospital claims registries in Japan, covering more than 30 million patients and including both inpatients and outpatients data regardless of the type of insurance[7] (all data are anonymized at the inclusion to the database; therefore, consent from each patient was not obtained in this study).

Patient Disposition and Data Collection

Patients with GERD aged 20 years or above were extracted from the database with the diagnosis record of RE or nonerosive reflux disease (NERD) of International Statistical Classification of Diseases and Related Health Problems (ICD)-10 code from April 1, 2015 to December 31, 2020. Patients were confirmed to have new prescription of PPI or P-CAB at the index date and at least 1-year medical record before the index date. Patients with active cancer, 7-day prescription of antibiotics regimen (prescription of PPI or P-CAB for *Helicobacter pylori* eradication) and prescription for prevention of ulcer by non-steroidal anti-inflammatory drugs or low-dose aspirin were excluded.

The overview of the data collected from each patient at the index date or during the observation periods were described in Supplementary Method 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A816). We identified health care costs as GERD-related costs (cost for therapeutic agents, endoscopy or X-ray examination, treatment of upper gastrointestinal bleeding, endoscopic treatment, and laparoscopic surgery) and hospitalization cost.

Definition of Patient Population, Cohort, and Subset

There were 4 subsets in each of PPI and P-CAB cohort: patients without dose change of PPI or P-CAB as subset 1, patients with dose change of PPI or P-CAB as subset 2, patients with intermittent treatment with PPI or P-CAB as subset 3, and patients with switching PPI to P-CAB or other medications in PPI cohort, P-CAB to PPI or other medications in P-CAB cohort (other medications include other esophageal medications, such as H2-receptor antagonist, esophageal mucosa protectant) as subset 4 (Fig. 1). A population including all subsets (subsets 1 to 4) was defined as the overall population. In addition, to investigate the medical costs in patients whose treatment was kept and unchanged, the analyses of "controlled population" that included the subsets 1 to 3 were performed. The "controlled population" was defined as the population of treatment success based on the following considerations: (1) RE

basically requires a long-term treatment including acid-suppressing agent as the main treatment option, (2) endoscopic findings of erosion healing were not recorded in the database and could not be directly evaluated, (3) no requirement for switching acid-suppressing agent could represent the cure or stabilization of symptoms with GERD.

From the consideration of generic use effect on therapeutic agent cost, esomeprazole (EPZ), an only PPI without available generic, was picked up for branded (nongeneric) PPI. The population of patients who received prescription of EPZ as the first-line treatment on the index date was defined as EPZ cohort, and the comparisons between EPZ cohort and P-CAB cohort were also performed as well as the comparisons between PPI cohort and P-CAB cohort.

Statistical Analysis

Propensity-score matching was used to minimize confounding factors for the comparison between 2 cohorts. Patients in PPI cohort and P-CAB cohort were matched with 1:1 ratio, using a caliper width of 0.1. The same matching method was applied to the patients in EPZ cohort and P-CAB cohort. The covariates for propensity-score matching were selected from the data obtained during the look-back period (12 mo before the index date) and at the index date.

The baseline demographic and clinical characteristics were descriptively summarized by cohorts (PPI vs. P-CAB cohort, EPZ vs. P-CAB cohort) for unmatched and matched cohorts in the overall population and controlled population. The standardized differences between cohorts were calculated for each item. We summarized detailed analysis method in Supplementary Method 2 (Supplemental Digital Content 1, http://links.lww.com/JCG/A816).

RESULTS

Patient Disposition and Baseline Characteristics

We identified a total of 3,528,994 patients with GERD, of which 3,511,311 (99.5%) were patients with RE. As the results from patients with RE were consistent with those from patients with GERD, including patients with NERD, hereafter, we described the results of patients with RE as a representative of patients with GERD. The results of patients with GERD, including both patients with RE and NERD, are shown in Supplementary Figure 1(A) and 1(B) (Supplemental Digital Content 1, http://links.lww.com/JCG/A816).

New users of PPI (n = 1,082,480) or P-CAB (n = 242,106) from a total of 3,511,311 patients with RE were identified and were subjected to 1:1 propensity-score matching in the overall population (n = 242,102, each) and controlled population (n = 151,541, each) (Fig. 2A). Similarly, new users of EPZ or P-CAB were matched by 1:1 in the overall population (n = 241,825, each) and controlled population (n = 151,355, each) (Fig. 2B).

The baseline characteristics such as age, medical history, and pretreatment were balanced between the treatment groups, with the standardized differences of <10% except for several characteristics (Table 1, Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A816). In the overall population, the mean patient age was 64.2 and 63.1 years in PPI and P-CAB matched cohort and 62.6 and 63.0 years in EPZ and P-CAB matched cohort, respectively. Males comprised 48.2% and 51.7% in PPI and P-CAB matched cohort and 44.6% and 51.7% in EPZ and P-CAB matched cohort, respectively (Table 1).

Health Care Costs

In the comparison of propensity-score matched cohorts, the mean 3-year cumulative health care cost including hospitalization cost per patient was higher with PPI than with P-CAB (¥142,620 vs. ¥122,444) (Fig. 3A, Table 2). In contrast, the cost was lower with EPZ than with P-CAB (¥105,263 vs. ¥121,958) (Fig. 3B, Table 3). In the analysis of the breakdown of expenses incurred, hospitalization cost comprised the highest proportion in the health care cost although the number of hospitalization events were at most 3332 (1.4%) in PPI and at least 1109 (0.46%) in EPZ in matched cohorts. Most of the hospitalization costs appeared to be unrelated to GERD treatment. In fact, GERD-triggered or RE-triggered hospitalization (patients with ICD-10 code of GERD, RE, and refractory RE requiring maintenance therapy) was 0.0% to 0.6% in all the hospitalization events. Of GERD-related diseases that caused hospitalization, upper gastrointestinal bleedings such as acute hemorrhage gastric ulcer (4.0% to 11.4%), hemorrhage gastric ulcer (2.4% to 5.7%) and acute hemorrhage duodenal ulcer (2.2% to 5.5%) were most frequently observed (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JCG/A816). When excluding hospitalization, the GERD-related cost (GERD-related cost consisted of therapeutic agent, upper gastrointestinal endoscopy, X-ray examination, treatment for upper gastrointestinal bleeding, and laparoscopic surgery cost) per patient became lower in patients with PPI than in those with P-CAB (¥44,777 vs. ¥71,783), and the cost with EPZ was consistently lower than that with P-CAB (¥58,264 vs. ¥71,771) (Table 2 and 3). Similar results were obtained from the analyses in the controlled population (Supplementary Table 3,

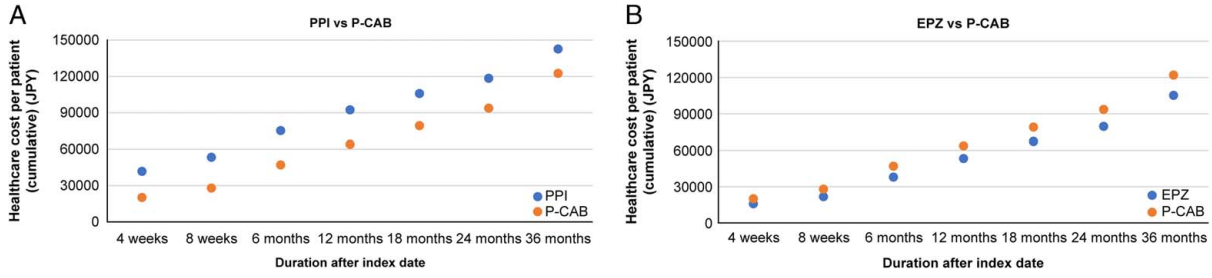

FIGURE 3. A, Health care cost in total per patient (cumulative cost after index date) [proton pump inhibitor (PPI) vs. potassium-competitive acid blocker (P-CAB), matched cohort, overall population, patients with reflux esophagitis]. B, Health care cost in total per patient (cumulative cost after index date) [esomeprazole (EPZ) vs. P-CAB, matched cohort, overall population, patients with reflux esophagitis).

TABLE 2. Health Care Costs Per Patient (Cumulative Cost After Index Date) (PPI vs. P-CAB, Matched Cohort, Overall Population, Patients With Reflux Esophagitis)

	4 wk			8 wk			6 mo		
	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)
GERD-related cost									
Therapeutic agents cost	3382	6065	−2684 (−2708.2 to −2663.8)	4796	8648	−3852 (−3890.4 to −3821.1)	9631	17,034	−7406 (−7487.3 to 7316.1)
Endoscopy or X-ray examination cost	1884	2420	−535 (−565.5 to −508.2)	2191	2775	−581 (−616.0 to −551.5)	2817	3448	−632 (−673.0 to −590.5)
Treatment cost for upper gastrointestinal bleeding	75	52	24 (17.3-30.0)	90	64	25 (17.0-33.6)	133	96	36 (22.9-48.9)
Endoscopic treatments cost	9	3	6 (5.4-6.6)	10	3	6 (5.4-7.0)	12	4	7 (6.1-8.1)
Laparoscopic surgery cost	855	306	549 (493.2-596.2)	916	403	513 (446.3-565.6)	1042	560	478 (400.4-547.0)
Hospitalization cost	36,786	11,700	25,039 (23,637.6—26,372.3)	46,760	16,564	30,046 (28,203.0-32,067.0)	63,029	26,614	36,337 (33,250.3-39,160.4)
Total cost	41,811	20,166	21,589 (20,201.2-22,931.9)	53,501	27,952	25,401 (23,541.2-27,389.5)	75,207	47,050	28,095 (25,013.5-30,928.5)

	12 mo			18 mo			24 mo		
	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)
GERD-related cost									
Therapeutic agents cost	15,504	27,022	−11,523 (−11,661.3 to −11,354.3)	21,001	36,354	−15,342 (−15,604.5 to −15,119.7)	26,307	45,333	−19,006 (−19,327.0 to −18,643.3)
Endoscopy or X-ray examination cost	3501	4177	−674 (−724.4 to −630.8)	4216	5006	−792 (−842.2 to −726.4)	4871	5759	−885 (−952.5 to −823.9)
Treatment cost for upper gastrointestinal bleeding	170	127	43 (26.9-58.8)	198	152	46 (21.9-66.7)	224	172	50 (24.5-71.9)
Endoscopic treatments cost	14	6	8 (6.9-9.5)	17	7	9 (7.7-11.3)	18	8	10 (8.3-12.3)
Laparoscopic surgery cost	1154	656	505 (404.7-569.9)	1232	750	481 (381.5-569.9)	1320	834	480 (367.7-579.2)
Hospitalization cost	73,611	32,888	40,819 (37,079.2-44,153.1)	80,974	37,964	43,003 (38,121.5-47,475.7)	87,562	42,806	44,609 (39,243.3-48,702.7)
Total cost	92,246	64,003	28,453 (24,702.2-31,676.0)	105,855	79,215	26,660 (21,832.0-31,098.5)	118,360	93,681	24,503 (19,092.0-28,691.1)

	36 mo		
	PPI (N = 242,102)	P-CAB (N = 242,102)	Difference (95% CI)
GERD-related cost			
Therapeutic agents cost	36,808	63,218	−26,415 (−26,896.5 to −25,867.8)
Endoscopy or X-ray examination cost	6191	7353	−1160 (−1244.0 to −1062.9)
Treatment cost for upper gastrointestinal bleeding	265	212	51 (24.1-79.6)
Endoscopic treatments cost	23	10	13 (10.2-15.7)
Laparoscopic surgery cost	1490	990	496 (330.9-597.7)
Hospitalization cost	100,062	51,836	48,179 (41,360.7-53,529.4)
Total cost	142,620	122,444	20,269 (13,781.3-25,925.9)

Cost unit is Japanese yen.

CI indicates confidence interval; GERD, gastroesophageal reflux disease; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

TABLE 3. Health Care Costs Per Patient (Cumulative Cost After Index Date) (EPZ vs. P-CAB, Matched Cohort, Overall Population, Patients With Reflux Esophagitis)

	4 wk			8 wk			6 mo		
	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)
GERD-related cost									
Therapeutic agents cost	4709	6066	−1357 (−1377.6 to −1336.1)	6723	8649	−1927 (−1957.9 to −1898.0)	13,606	17,039	−3430 (−3514.0 to −3349.3)
Endoscopy or X-ray examination cost	2090	2421	−328 (−367.4 to −304.8)	2381	2774	−391 (−436.3 to −364.7)	2958	3447	−489 (−535.9 to −453.2)
Treatment cost for upper gastrointestinal bleeding	34	52	−18 (−23.2 to −11.1)	46	64	−18 (−25.7 to −10.5)	73	95	−23 (−37.8 to −8.5)
Endoscopic treatments cost	2	3	−1 (−0.8 to −0.4)	2	3	−1 (−1.4 to −0.5)	4	5	0 (−1.2 to 0.8)
Laparoscopic surgery cost	166	300	−134 (−171.2 to −92.3)	207	398	−193 (−240.2 to −143.4)	311	557	−243 (−311.3 to −185.7)
Hospitalization cost	8960	11,595	−2698 (−3742.6 to −1486.9)	12,696	16,472	−3785 (−5025.7 to −2486.2)	21,310	26,422	−5184 (−7234.0 to −3554.8)
Total cost	15,752	20,055	−4351 (−5410.2 to −3175.0)	21,778	27,876	−6072 (−7324.2 to −4802.5)	37,817	46,856	−9081 (−11,083.5 to −7412.5)

	12 mo			18 mo			24 mo		
	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)
GERD-related cost									
Therapeutic agents cost	21,846	27,011	−5171 (−5308.8 to −5025.6)	29,505	36,344	−6852 (−7151.3 to −6647.1)	36,801	45,300	−8513 (−8976.2 to −8203.7)
Endoscopy or X-ray examination cost	3614	4174	−558 (−605.7 to −497.4)	4352	5007	−653 (−721.1 to −590.4)	5014	5757	−740 (−815.1 to −663.6)
Treatment cost for upper gastrointestinal bleeding	98	128	−29 (−45.8 to −11.1)	119	151	−31 (−48.6 to −8.5)	138	172	−34 (−52.2 to −8.7)
Endoscopic treatments cost	6	6	−1 (−2.0 to 0.7)	7	7	−1 (−2.0 to 0.8)	8	8	0 (−1.7 to 1.5)
Laparoscopic surgery cost	394	652	−254 (−322.1 to −187.5)	447	749	−295 (−381.0 to −217.9)	509	834	−323 (−417.9 to −236.4)
Hospitalization cost	27,815	32,623	−4828 (−7671.2 to −2189.8)	33,398	37,639	−4352 (−9249.3 to −1006.4)	37,801	42,597	−4602 (−9771.7 to −991.4)
Total cost	53,238	63,677	−10,481 (−13,319.8 to −7946.6)	67,201	78,999	−11,813 (−16,732.0 to −8354.1)	79,611	93,515	−13,772 (−19,034.2 to −10,130.2)

	36 mo		
	Esomeprazole (N = 241,825)	P-CAB (N = 241,825)	Difference (95% CI)
GERD-related cost			
Therapeutic agents cost	51,018	63,203	−12,238 (−12,787.7 to −11,644.8)
Endoscopy or X-ray examination cost	6413	7353	−935 (−1038.5 to −819.4)
Treatment cost for upper gastrointestinal bleeding	181	212	−32 (−57.0 to −0.9)
Endoscopic treatments cost	10	10	0 (−2.2 to 2.0)
Laparoscopic surgery cost	642	993	−346 (−451.0 to −228.4)
Hospitalization cost	47,873	51,545	−4203 (−9891.0 to 61.4)
Total cost	105,263	121,958	−17,304 (−23,078.8 to −13,162.9)

Cost unit is Japanese yen.
CI indicates confidence interval; EPZ, esomeprazole; GERD, gastroesophageal reflux disease; P-CAB, potassium-competitive acid blocker.

TABLE 4. Percentage of Keeping Initial Treatment (Matched Cohort, Overall Population, and Patients With Reflux Esophagitis)

PPI	Index Date	4 wk	8 wk	6 mo	12 mo	18 mo	24 mo	36 mo	All
Number of at risk	242,102	113,668	91,581	61,603	42,925	31,136	22,815	12,237	0
Number of event*	38,805	104,974	121,778	142,716	154,217	160,693	164,868	169,473	173,102
Keeping rate† (95% CI)	84.0 (83.82-84.12)	53.8 (53.61-54.02)	45.6 (45.41-45.83)	34.6 (34.38-34.79)	27.7 (27.49-27.89)	23.2 (23.03-23.42)	19.9 (19.67-20.06)	15.2 (15.00-15.38)	5.4 (4.35-6.52)
P-CAB	**Index Date**	**4 wk**	**8 wk**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**All**
Number of at risk	242,102	104,322	79,370	47,197	28,861	18,110	11,358	4069	0
Number of event*	40,250	107,920	127,209	150,519	162,146	168,369	171,663	174,844	176,109
Keeping rate† (95% CI)	83.4 (83.23-83.52)	51.4 (51.22-51.65)	41.6 (41.34-41.77)	28.5 (28.31-28.71)	20.9 (20.71-21.09)	16.0 (15.80-16.16)	12.7 (12.54-12.89)	8.2 (8.05-8.40)	1.2 (0.48-2.58)

*Prescription of any acid-suppressing drugs other than initial treatment, first discontinuation of initial treatment, having GERD-related esophageal or gastroduodenal surgery.
†Proportion of patients without any events.
CI indicates confidence interval; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Supplemental Digital Content 1, http://links.lww.com/JCG/A816 and Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/JCG/A816).

Treatment Patterns

The percentage of keeping initial treatment at 8 weeks, 12 months, and 36 months after index date were 45.6%, 27.7%, and 15.2% in PPI and 41.6%, 20.9%, and 8.2% in P-CAB, respectively (Table 4 and Fig. 4). The switching rate from initial PPI to P-CAB at 8 weeks, 12 months, and 36 months after index date were 3.5%, 7.5%, and 15.9%, respectively. In contrast, the switching rates from initial P-CAB to PPI at the same time points were 7.5%, 20.2%, and 40.8%, respectively. In addition, in the matched cohorts, switching rates during hospitalization from branded PPI or P-CAB to generic PPI were 11.3% and 27.0%, respectively, and that from EPZ or P-CAB to generic PPI were 41.9% versus 26.9%, respectively (Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/JCG/A816). The discontinuation rates of initial PPI were comparable with those of P-CAB at 8 weeks, 12 months, and 36 months (34.3% vs. 35.7%, 52.3% vs. 56.1%, and 65.5% vs. 70.7%, respectively) (Table 5). Under the treatment patterns, the occurrence of severe GERD-related complications was also comparable between PPI and P-CAB at 8 weeks, 12 months, and 36 months (2.5% vs. 1.7%, 3.5% vs. 2.5%, and 4.8% vs. 3.8%, respectively) (Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/JCG/A816 and Supplementary Figure 2, Supplemental Digital Content 1, http://links.lww.com/JCG/A816).

DISCUSSION

GERD is a typical acid-related disorder in which PPIs and P-CAB are used as first-line treatment owing to their gastric acid secretory suppressive effect. Because GERD requires long-term management owing to repeated relapses, favorable treatment models have been investigated in terms of health care costs as well as efficacy and safety of therapeutic agents. Recent studies have reported that P-CAB, a potent gastric antisecretory agent, can reduce health care costs and is more cost effective than PPIs, such as EPZ and rabeprazole, by developing a model using healing and relapse rates of therapeutic agents.[5] However, our study based on real-world data showed an inconsistent result with the model-based prediction that there was no obvious cost benefit of P-CAB-first treatment compared with EPZ-first or PPIs-first treatments, especially in GERD-related costs except hospitalization cost.

Although contribution of hospitalization cost was the largest in health care cost in this study, the percentage of GERD-triggered hospitalization was minimal (0.0% to 0.6%) in which upper gastrointestinal bleedings (2.2% to 12.4%) were most frequently observed (Supplemental Table S2, Supplemental Digital Content 1, http://links.lww.com/JCG/A816). At least, GERD was not a major driver of hospitalization costs. In other words, it is unlikely that the hospitalization costs and the number of hospitalizations in this study are because of the therapeutic effects of PPI, EPZ, and P-CAB. Because previous studies using Markov model did not apply hospitalization costs in the analysis, when excluding the effect of the hospitalization costs from our health care costs, the 3-year GERD-related cost in patients with PPI and P-CAB resulted in ¥44,777 and ¥71,783, respectively. Similar 3-year result can be seen in a comparison between propensity-score matched EPZ and P-CAB

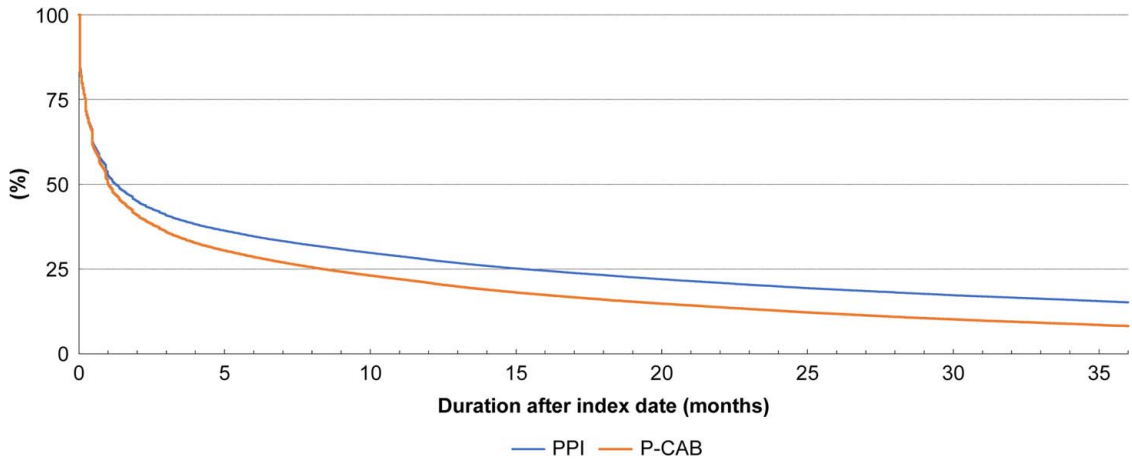

FIGURE 4. Percentage of keeping initial treatment [proton pump inhibitor (PPI) vs. potassium-competitive acid blocker (P-CAB), matched cohort, overall population, patients with reflux esophagitis]. The first discontinuation of initial treatment was treated as an event. Patients without discontinuation of initial treatment were censored at the date of last available record in the database.

cohorts (¥58,264 and ¥71,771, respectively). Considering the fact that therapeutic agent cost had the largest impact (approximately 80% to 90%) other than hospitalization cost, it would be reasonable to suggest that drug price is the most important determinant for health care costs except hospitalization in real-world settings.

Regarding higher hospitalization costs in PPI users than in EPZ or P-CAB [which can be restated as vonoprazan (VPZ)] users, we assume that health care reimbursement system affected the results. The database we used was created using patient data from hospitals which have applied per-diem payment system called "diagnosis procedure combination (DPC)," a system in which provider reimbursement is calculated based on a flat-rate per-diem fee based on the diagnosis group.[8] Accordingly, it is possible that physicians or patients intentionally selected inexpensive PPIs to manage total health care cost or out of pocket payment. In fact, 11.3% to 41.9% of patients switched treatment agent to generic PPI from brand PPI or P-CAB at the time of admission of the patients.

Our findings from real-world health care costs were different from those previously reported based on Markov simulation model. Habu[4] reported that the initiation of P-CAB for acute medical treatment of RE would show better cost-effectiveness than initiation of PPI owing to shorter period of the required treatment. Using the Markov model, Yokoya et al[5] also reported that the 5-year expected costs for GERD treatment by VPZ, EPZ, and rabeprazole-first strategies were ¥36,194, ¥76,719, and ¥41,105, respectively, using estimated costs for medication, outpatient visit, and endoscopy. The discrepancy of medical cost between P-CAB initial treatment model and actual clinical practice might be explained by the different assumption of treatment course. In the model analysis,[4,5] the cost was calculated based on differences in healing and relapse rate of RE between P-CAB and PPI using data from the prospective comparative study[9,10] and network meta-analysis.[11,12] For instance, the authors applied the assumption that unhealed patients with moderate to severe RE was 15% higher in PPI users than in P-CAB users at 4 weeks[9] and PPI users has 9% to 30% higher relapse rate during 6-month maintenance treatment than P-CAB users.[12] Accordingly, the benefit of shorter treatment period and related reduction in medication, examination, and visiting costs by switching from PPI to P-CAB was incorporated into the model. However, in the real-world, unlike patients in prospective interventional studies, >90% of patients have mild-to-moderate GERD in Japan as previously reported.[7] It was also supported by the results that the proportions of patients whose initial treatment were kept (ie, who were likely to be well treated) were 45.6% in PPI cohort and 41.6 % in P-CAB cohort at 8 weeks and 27.7% in PPI cohort and 20.9% in P-CAB cohort at 12 months and, as a consequence, the switch rates from PPIs and EPZ to P-CAB were lower than the assumption of model analyses. In other words, the discrepancy might be caused by different healing and relapse rate between clinical study setting and actual clinical practice.

There are some limitations in this database study. First, endoscopic findings of RE and patient's reported outcome, such as subjective symptom, quality of life which were usually assessed in clinical study were not available in the database. Second, number of NERD were only 0.5% in this study. It was too low when compared with the report that more than half of GERD was NERD under endoscopic examination by epidemiological survey.[7] Third, the database used in this study does not include the data from primary care hospitals, mainly include the data from secondary care hospitals, so the results of this study may not represent the data of the overall population of patients with GERD. Fourth, patients cannot be followed up when they were transferred to other health care facilities. Fifth, a long-term prescription of VPZ was not allowed under Japanese regulation in 2015, although there was no such limitation for PPI prescription. Last, some discrepancy of patients' age and gender were found between matched cohort of PPI/P-CAB and EPZ/P-CAB. Although there were these limitations of the database, the results of our study better reflected the actual clinical practice in terms of costs related to the treatment of GERD than the previously reported results.

CONCLUSIONS

Health care cost was higher in patients with GERD initiated on PPI than in those initiated on P-CAB mainly owing to non-GERD-related hospitalization cost, whereas it was lower in those initiated on EPZ than in those initiated on P-CAB. When considering health care costs except hospitalization costs, PPI-first treatment was less expensive than

TABLE 5. Discontinuation Rate of Initial Treatment (Matched Cohort, Overall Population, Patients With Reflux Esophagitis)

PPI	Index Date	4 wk	8 wk	6 mo	12 mo	18 mo	24 mo	36 mo	All
Number of at risk	242,102	133,029	107,599	72,460	51,106	37,198	27,148	14,465	0
Number of event*	1969	49,421	64,654	81,815	89,683	94,013	96,646	99,579	101,994
Discontinuation rate (95% CI)	0.8 (0.78-0.85)	25.3 (25.13-25.51)	34.3 (34.05-34.48)	45.7 (45.51-45.99)	52.3 (52.03-52.53)	56.7 (56.48-57.00)	60.2 (59.90-60.45)	65.5 (65.20-65.80)	80.5 (78.24-82.71)
P-CAB	**Index Date**	**4 wk**	**8 wk**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**All**
Number of at risk	242,102	136,053	105,707	65,015	41,867	27,395	17,723	6708	0
Number of event*	1543	50,836	68,243	87,627	95,765	100,003	102,146	104,283	105,141
Discontinuation rate (95% CI)	0.6 (0.61-0.67)	25.6 (25.38-25.76)	35.7 (35.44-35.87)	48.9 (48.63-49.12)	56.1 (55.89-56.40)	61.2 (60.94-61.48)	64.8 (64.49-65.05)	70.7 (70.40-71.07)	84.5 (81.26-87.49)

*Discontinuation of initial treatment.
CI indicates confidence interval; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

P-CAB-first treatment. Although the reasons for higher hospitalization cost in PPI cohorts need to be further investigated, considering the higher switching rate to generic PPIs during hospitalization and the DPC reimbursement system, it is highly likely that inexpensive PPIs were selected to manage total health care cost burden during hospitalization. While we could not validate the accuracy of the model-based cost prediction, differences in the assumption of treatment patterns, such as low switching rate from PPIs to P-CAB, and the severity of patients with GERD in the real-world settings may partially explain the discrepancy between the prediction and actual cost.

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