Supplementary Method 1. Data collected from each patient at the index date or during the observation periods

Data collected from each patient at the index date or during the observation periods were as follows: demographic information (age [at the index date], gender [either of the look-back period or the index date]), endoscopic examination, medical history, history of hospitalization, and treatment provided (during the look-back period), healthcare costs, resource use, and other outcomes (during the follow-up period).

With respect to the healthcare costs, we defined the following costs as healthcare costs: GERD-related costs, including cost for therapeutic agents (including proton pump inhibitor [PPI] or P-CAB and other therapeutic agents for upper gastrointestinal disease), cost for endoscopy or X-ray examination (on esophagus or gastroduodenum), cost for treatment of upper gastrointestinal bleeding (with hemostatic agents), cost for endoscopic treatment (of upper gastrointestinal bleeding or gastrointestinal surgery conducted), and cost for laparoscopic surgery (and any surgery related to GERD including esophageal hiatal hernia), and hospitalization cost.

In addition, to assess the clinical measures for GERD by percentage of keeping initial treatment of GERD (defined as the percentage of patients who continued the initial acid-suppressing agent or became free from any acid-suppressing agents without requiring GERD-related surgical or endoscopic treatment) and occurrence of severe GERD-related complication (defined as upper gastrointestinal bleeding or esophageal or gastroduodenal surgery and endoscopic treatment during follow-up period), the data of continuation or discontinuation status of acid-suppressing agents, presence or absence of surgical or endoscopic treatment of GERD, and presence or absence of upper gastrointestinal bleeding or surgical upper gastrointestinal treatment were collected. Moreover, to assess the treatment pattern of acid-suppressing agents, more detailed prescription information including dose, regimen, time to discontinuation, switching, dose increase or reduction were also collected.

Supplementary Method 2. Analysis Method

For the GERD-related healthcare costs, mean cumulative cost by items per patient was calculated for each duration after the index date (4 and 8 weeks, 6, 12, 18, 24, and 36 months). The calculation of mean cumulative costs per patient was performed according to the following procedures: (1) summing up the costs per patient on each day, (2) summing up (1) for the relevant duration (Day 1–Day k), (3) dividing (2) by the number of analyzed patients on the database on Day k. The difference between cohorts of the GERD-related healthcare costs per patient was estimated using nonparametric bootstrap iterations with 95% confidence interval.

The percentage of keeping initial treatment was summarized for each duration after the index date (4 and 8 weeks, 6, 12, 18, 24, and 36 months). In addition, the percentage of keeping initial treatment was analyzed using Kaplan–Meier method. The first discontinuation of initial treatment was treated as event. Patients without discontinuation of initial treatment were censored at the date of last available record in the database.

The incidence rate of severe GERD-related complication was summarized for each duration after the index date (4 and 8 weeks, 6, 12, 18, 24, and 36 months). In addition, cumulative occurrence of severe GERD-related complication was analyzed using Kaplan–Meier method. The first occurrence of severe GERD-related complication was treated as event. Patients without severe GERD-related complication were censored at the date of last available record in the database.

For the assessment of treatment patterns and factors, the time to switching including discontinuation was analyzed using Kaplan–Meier method.

There were switching patterns, such as PPI to other PPI, PPI to P-CAB, PPI discontinuation, PPI to H2-receptor antagonist, P-CAB to PPI, P-CAB discontinuation, and P-CAB to H2-receptor antagonist. Number of patients switched to generic PPI from brand PPI or P-CAB and number of those patients in hospital and in an ambulatory setting were also analyzed additionally.

Supplementary Table 1: Baseline demographic and clinical characteristic (controlled population, patients with reflux esophagitis)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Unmatched cohort | | | | Matched cohort | | | Unmatched cohort | | | Matched cohort | | |
|  | PPI (N=697214) | | P-CAB (N=151541) | SD  (%) | PPI (N=  151541) | P-CAB (N=151541) | SD  (%) | Esomeprazole (N=255342) | P-CAB (N=151541) | SD(%) | Esomeprazole (N=  151355) | P-CAB (N=151355) | SD  (%) |
| Age, years |  | |  |  |  |  |  |  |  |  |  |  |  |
| mean (SD) | 63.2 (18.1) | | 61.5 (17.5) | 10.0 | 64.3 (17.4) | 61.5 (17.5) | 16.5 | 60.4 (17.9) | 61.5 (17.5) | −5.8 | 60.2 (17.9) | 61.4 (17.5) | −6.8 |
| Gender |  | |  |  |  |  |  |  |  |  |  |  |  |
| male | 355538 (51.0) | | 80114 (52.9) | −3.7 | 79583 (52.5) | 80114 (52.9) | −0.7 | 130688 (51.2) | 80114 (52.9) | −3.4 | 75120 (49.6) | 79969 (52.8) | −6.4 |
| female | 341676 (49.0) | | 71427 (47.1) |  | 71958 (47.5) | 71427 (47.1) |  | 124654 (48.8) | 71427 (47.1) |  | 76235 (50.4) | 71386 (47.2) |  |
| Endoscopic examination |  | |  |  |  |  |  |  |  |  |  |  |  |
| mean (SD) | 0.1 (0.2) | | 0.1 (0.3) | −3.7 | 0.1 (0.2) | 0.1 (0.3) | −2.3 | 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 | 918 (0.1) | | 293 (0.2) | −1.5 | 248 (0.2) | 293 (0.2) | −0.7 | 390 (0.2) | 293 (0.2) | −1.0 | 269 (0.2) | 291 (0.2) | −0.3 |
| Hiatus hernia | 4647 (0.7) | | 1179 (0.8) | −1.3 | 1104 (0.7) | 1179 (0.8) | −0.6 | 1731 (0.7) | 1179 (0.8) | −1.2 | 1114 (0.7) | 1178 (0.8) | −0.5 |
| Chronic pharyngitis | 49877 (7.2) | | 10855 (7.2) | 0.0 | 14883 (9.8) | 10855 (7.2) | 9.5 | 21250 (8.3) | 10855 (7.2) | 4.3 | 13425 (8.9) | 10854 (7.2) | 6.3 |
| Sleep disorders | 77077 (11.1) | | 14503 (9.6) | 4.9 | 17960 (11.9) | 14503 (9.6) | 7.4 | 25436 (10.0) | 14503 (9.6) | 1.3 | 15092 (10.0) | 14484 (9.6) | 1.4 |
| Scleroderma | 1759 (0.3) | | 360 (0.2) | 0.3 | 507 (0.3) | 360 (0.2) | 1.8 | 657 (0.3) | 360 (0.2) | 0.4 | 393 (0.3) | 359 (0.2) | 0.5 |
| Gastric ulcer | 83860 (12.0) | | 18815 (12.4) | −1.2 | 25927 (17.1) | 18815 (12.4) | 13.3 | 31129 (12.2) | 18815 (12.4) | −0.7 | 17006 (11.2) | 18760 (12.4) | −3.6 |
| Duodenal ulcer | 4200 (0.6) | | 1185 (0.8) | −2.2 | 1383 (0.9) | 1185 (0.8) | 1.4 | 1485 (0.6) | 1185 (0.8) | −2.4 | 1113 (0.7) | 1180 (0.8) | −0.5 |
| Anastomotic ulcer | 42 (0.0) | | 9 (0.0) | 0.0 | 7 (0.0) | 9 (0.0) | −0.2 | 19 (0.0) | 9 (0.0) | 0.2 | 11 (0.0) | 9 (0.0) | 0.2 |
| Gastritis and duodenitis | 113228 (16.2) | | 27122 (17.9) | −4.4 | 27927 (18.4) | 27122 (17.9) | 1.4 | 47675 (18.7) | 27122 (17.9) | 2.0 | 30330 (20.0) | 27109 (17.9) | 5.4 |
| Upper gastrointestinal bleeding, Hematemesis, Bloody stool | | 8360 (1.2) | 1279 (0.8) | 3.5 | 1675 (1.1) | 1279 (0.8) | 2.7 | 2043 (0.8) | 1279 (0.8) | −0.5 | 1342 (0.9) | 1275 (0.8) | 0.5 |
| H. pylori infection | | 7438 (1.1) | 2172 (1.4) | −3.3 | 2030 (1.3) | 2172 (1.4) | −0.8 | 3324 (1.3) | 2172 (1.4) | −1.1 | 2101 (1.4) | 2171 (1.4) | −0.4 |
| Crohn's disease | | 1262 (0.2) | 174 (0.1) | 1.7 | 205 (0.1) | 174 (0.1) | 0.6 | 525 (0.2) | 174 (0.1) | 2.3 | 230 (0.2) | 173 (0.1) | 1.0 |
| Ulcerative colitis | | 5461 (0.8) | 857 (0.6) | 2.7 | 1070 (0.7) | 857 (0.6) | 1.8 | 2510 (1.0) | 857 (0.6) | 4.8 | 1039 (0.7) | 856 (0.6) | 1.5 |
| Myocardial infarction | | 23721 (3.4) | 6768 (4.5) | −5.5 | 5196 (3.4) | 6768 (4.5) | −5.3 | 7464 (2.9) | 6768 (4.5) | −8.2 | 5987 (4.0) | 6635 (4.4) | −2.1 |
| Stroke | | 34560 (5.0) | 6280 (4.1) | 3.9 | 6677 (4.4) | 6280 (4.1) | 1.3 | 8261 (3.2) | 6280 (4.1) | −4.8 | 5801 (3.8) | 6234 (4.1) | −1.5 |
| Obesity | | 2550 (0.4) | 554 (0.4) | 0.0 | 709 (0.5) | 554 (0.4) | 1.6 | 880 (0.3) | 554 (0.4) | −0.4 | 553 (0.4) | 554 (0.4) | 0.0 |
| Peripheral vascular disease | | 1850 (0.3) | 344 (0.2) | 0.8 | 442 (0.3) | 344 (0.2) | 1.3 | 534 (0.2) | 344 (0.2) | −0.4 | 319 (0.2) | 342 (0.2) | −0.3 |
| Cerebrovascular disease | | 5799 (0.8) | 1520 (1.0) | −1.8 | 1625 (1.1) | 1520 (1.0) | 0.7 | 1656 (0.6) | 1520 (1.0) | −3.9 | 1324 (0.9) | 1504 (1.0) | −1.2 |
| Dementia | 29294 (4.2) | | 4105 (2.7) | 8.2 | 4438 (2.9) | 4105 (2.7) | 1.3 | 6373 (2.5) | 4105 (2.7) | −1.3 | 3845 (2.5) | 4094 (2.7) | −1.0 |
| Asthma | 45719 (6.6) | | 8352 (5.5) | 4.4 | 10330 (6.8) | 8352 (5.5) | 5.4 | 18215 (7.1) | 8352 (5.5) | 6.7 | 9599 (6.3) | 8351 (5.5) | 3.5 |
| Chronic pulmonary disease | 71761 (10.3) | | 12921 (8.5) | 6.1 | 16135 (10.6) | 12921 (8.5) | 7.2 | 27388 (10.7) | 12921 (8.5) | 7.5 | 14832 (9.8) | 12919 (8.5) | 4.4 |
| Collagen disease | 3038 (0.4) | | 586 (0.4) | 0.8 | 806 (0.5) | 586 (0.4) | 2.1 | 1174 (0.5) | 586 (0.4) | 1.1 | 722 (0.5) | 585 (0.4) | 1.4 |
| Liver disease | 33477 (4.8) | | 6513 (4.3) | 2.4 | 8173 (5.4) | 6513 (4.3) | 5.1 | 13011 (5.1) | 6513 (4.3) | 3.8 | 7335 (4.8) | 6510 (4.3) | 2.6 |
| Hemiplegia | 13384 (1.9) | | 2320 (1.5) | 3.0 | 2607 (1.7) | 2320 (1.5) | 1.5 | 3462 (1.4) | 2320 (1.5) | −1.5 | 2257 (1.5) | 2285 (1.5) | −0.2 |
| Any tumor | 112 (0.0) | | 0 (0.0) | 1.8 | 0 (0.0) | 0 (0.0) | - | 37 (0.0) | 0 (0.0) | 1.7 | 0 (0.0) | 0 (0.0) | - |
| Leukemia | 3 (0.0) | | 0 (0.0) | 0.3 | 0 (0.0) | 0 (0.0) | - | 0 (0.0) | 0 (0.0) | - | 0 (0.0) | 0 (0.0) | - |
| Metastatic solid tumor | 8 (0.0) | | 0 (0.0) | 0.5 | 0 (0.0) | 0 (0.0) | - | 3 (0.0) | 0 (0.0) | 0.5 | 0 (0.0) | 0 (0.0) | - |
| AIDS | 400 (0.1) | | 62 (0.0) | 0.7 | 91 (0.1) | 62 (0.0) | 0.9 | 138 (0.1) | 62 (0.0) | 0.6 | 86 (0.1) | 62 (0.0) | 0.7 |
| AF or atrial flutter | 71892 (10.3) | | 15497 (10.2) | 0.3 | 15197 (10.0) | 15497 (10.2) | −0.7 | 24600 (9.6) | 15497 (10.2) | −2.0 | 15850 (10.5) | 15487 (10.2) | 0.8 |
| Valvular heart disease | 31628 (4.5) | | 6134 (4.0) | 2.4 | 6764 (4.5) | 6134 (4.0) | 2.1 | 9548 (3.7) | 6134 (4.0) | −1.6 | 5966 (3.9) | 6124 (4.0) | −0.5 |
| Esophageal surgery/ endoscopic treatment/examination | 9118 (1.3) | | 1758 (1.2) | 1.3 | 1793 (1.2) | 1758 (1.2) | 0.2 | 3365 (1.3) | 1758 (1.2) | 1.4 | 1941 (1.3) | 1757 (1.2) | 1.1 |
| Gastroduodenal surgery/ endoscopic treatment/examination | 45339 (6.5) | | 10698 (7.1) | −2.2 | 10047 (6.6) | 10698 (7.1) | −1.7 | 19386 (7.6) | 10698 (7.1) | 2.0 | 11565 (7.6) | 10694 (7.1) | 2.2 |
| History of hospitalization | 167566 (24.0) | | 29356 (19.4) | 11.3 | 32837 (21.7) | 29356 (19.4) | 5.7 | 51814 (20.3) | 29356 (19.4) | 2.3 | 31155 (20.6) | 29344 (19.4) | 3.0 |
| Emergency visit | 90232 (12.9) | | 15669 (10.3) | 8.1 | 16960 (11.2) | 15669 (10.3) | 2.7 | 24589 (9.6) | 15669 (10.3) | −2.4 | 15004 (9.9) | 15665 (10.3) | −1.4 |
| ICU admission | 23101 (3.3) | | 5206 (3.4) | −0.7 | 4934 (3.3) | 5206 (3.4) | −1.0 | 6035 (2.4) | 5206 (3.4) | −6.4 | 4459 (2.9) | 5197 (3.4) | −2.8 |
| Pretreatment |  | |  |  |  |  |  |  |  |  |  |  |  |
| H2-RA | 42406 (6.1) | | 8626 (5.7) | 1.7 | 9370 (6.2) | 8626 (5.7) | 2.1 | 14884 (5.8) | 8626 (5.7) | 0.6 | 8936 (5.9) | 8622 (5.7) | 0.9 |
| M-RA | 15 (0.0) | | 4 (0.0) | −0.1 | 3 (0.0) | 4 (0.0) | −0.1 | 4 (0.0) | 4 (0.0) | −0.2 | 2 (0.0) | 4 (0.0) | −0.3 |
| Antacid | 33308 (4.8) | | 7765 (5.1) | −1.6 | 7611 (5.0) | 7765 (5.1) | −0.5 | 14136 (5.5) | 7765 (5.1) | 1.8 | 8464 (5.6) | 7763 (5.1) | 2.1 |
| Esophageal/gastric mucosa protectants | 74975 (10.8) | | 15929 (10.5) | 0.8 | 17528 (11.6) | 15929 (10.5) | 3.4 | 28492 (11.2) | 15929 (10.5) | 2.1 | 17356 (11.5) | 15925 (10.5) | 3.0 |
| Prokinetic agents | 46503 (6.7) | | 10205 (6.7) | −0.3 | 10569 (7.0) | 10205 (6.7) | 1.0 | 17150 (6.7) | 10205 (6.7) | −0.1 | 10212 (6.7) | 10201 (6.7) | 0.0 |
| Antiplatelets | 77729 (11.1) | | 16847 (11.1) | 0.1 | 17114 (11.3) | 16847 (11.1) | 0.6 | 24302 (9.5) | 16847 (11.1) | −5.3 | 15250 (10.1) | 16835 (11.1) | −3.4 |
| Anticoagulants | 38167 (5.5) | | 8940 (5.9) | −1.8 | 8502 (5.6) | 8940 (5.9) | −1.2 | 13760 (5.4) | 8940 (5.9) | −2.2 | 8162 (5.4) | 8933 (5.9) | −2.2 |
| NSAIDs/Aspirin | 141845 (20.3) | | 29069 (19.2) | 2.9 | 32059 (21.2) | 29069 (19.2) | 4.9 | 49697 (19.5) | 29069 (19.2) | 0.7 | 30638 (20.2) | 29056 (19.2) | 2.6 |
| Total healthcare cost (in 3 months before the index date) |  | |  |  |  |  |  |  |  |  |  |  |  |
| n | 446634 | | 92828 | 3.4 | 92828 | 92828 | 0.0 | 159514 | 92828 | −2.9 | 92815 | 92815 | −0.5 |
| mean (SD) | 333793.27 (613348.26) | | 312955.98 (622456.40) |  | 313238.51 (604802.23) | 312955.98 (622456.40) |  | 295724.55 (576709.82) | 312955.98 (622456.40) |  | 309952.47 (597881.77) | 312861.75 (622343.17) |  |
| Total healthcare cost (in 12 months before the index date) |  | |  |  |  |  |  |  |  |  |  |  |  |
| n | 488466 | | 103184 | 2.9 | 116016 | 103184 | −4.2 | 177083 | 103184 | −2.3 | 106826 | 103142 | −2.2 |
| mean (SD) | 436172.60 (845841.18) | | 411328.57 (870905.12) |  | 375546.70 (822784.68) | 411328.57 (870905.12) |  | 392165.90 (798129.63) | 411328.57 (870905.12) |  | 392971.45 (799857.94) | 411285.44 (870849.99) |  |

SD: Standardized difference

Supplementary Table 2: Diseases that triggered hospitalization (matched cohort, overall population, patients with reflux esophagitis)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | PPI  N=242102 | P-CAB  N=242102 | Esomeprazole  N=241825 | P-CAB  N=241825 |
| Number of hospitalization | 3332 | 1573 | 1109 | 1568 |
| Number of event (% of total hospitalization event) |  |  |  |  |
| Dieulafoy ulcer | 14 (0.4) | 2 (0.1) | 3 (0.3) | 2 (0.1) |
| Parkinson's disease | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute alcoholic hepatitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute anterior apical myocardial infarction | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| acute anterior myocardial infarction | 4 (0.1) | 2 (0.1) | 4 (0.4) | 2 (0.1) |
| acute anteroseptal infarct | 6 (0.2) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| acute blood loss anemia | 4 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| acute drug intoxication | 1 (0.0) | 0 (0.0) | |  | | --- | | 0 (0.0) | | 0 (0.0) |
| acute duodenal ulcer | 6 (0.2) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| acute duodenal ulcer perforation | 71 (2.1) | 1 (0.1) | 5 (0.5) | 1 (0.1) |
| acute exacerbation of chronic obstructive pulmonary disease | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| acute extensive anterior myocardial infarction | 1 (0.0) | 2 (0.1) | 1 (0.1) | 2 (0.1) |
| acute gastric mucosal lesion | 5 (0.2) | 4 (0.3) | 3 (0.3) | 4 (0.3) |
| acute gastric ulcer | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| acute gastric ulcer perforation | 9 (0.3) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| acute gastritis | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| acute hemorrhagic duodenal ulcer | 183 (5.5) | 38 (2.4) | 32 (2.9) | 35 (2.2) |
| acute hemorrhagic duodenal ulcer perforation | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute hemorrhagic gastric ulcer | 380 (11.4) | 109 (6.9) | 44 (4.0) | 108 (6.9) |
| acute hemorrhagic gastric ulcer perforation | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute inferior infarction | 3 (0.1) | 6 (0.4) | 1 (0.1) | 6 (0.4) |
| acute inferior posterior myocardial infarction | 3 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| acute lateral myocardial infarction | 1 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| acute myocardial infarction | 1 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| acute posterior myocardial infarction | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute posterolateral myocardial infarction | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| acute subendocardial myocardial infarction | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| alcoholic cirrhosis | 8 (0.2) | 2 (0.1) | 3 (0.3) | 2 (0.1) |
| alcoholic hepatic failure | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| alcoholic hepatitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| alcoholic liver disorder | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| anastomotic ulcer hemorrhage | 27 (0.8) | 3 (0.2) | 2 (0.2) | 3 (0.2) |
| aneurysm of sinus of Valsalva | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| aortic valve incompetence | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| aortic valve stenosis | 4 (0.1) | 5 (0.3) | 2 (0.2) | 5 (0.3) |
| aortic valve stenosis and insufficiency | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| asthmatic attack | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| atrial fibrillation | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| bronchial asthma | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| bronchitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| cerebral infarction | 2 (0.1) | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| cerebral infarction - acute stage | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| chest pain | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| chronic atrial fibrillation | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| chronic gastric ulcer | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| chronic obstructive pulmonary disease | 1 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| cirrhosis type C | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| cryptogenic organizing pneumonitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| decompensated alcoholic cirrhosis | 2 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| decompensated liver cirrhosis | 0 (0.0) | 2 (0.1) | 2 (0.2) | 2 (0.1) |
| dementia | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| diabetic gangrene | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| diaphragmatic hernia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| drug-induced esophagus ulcer | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| drug-induced hepatitis | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| duodenal cancer | 2 (0.1) | 1 (0.1) | 3 (0.3) | 1 (0.1) |
| duodenal erosions | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| duodenal perforation | 20 (0.6) | 2 (0.1) | 1 (0.1) | 2 (0.1) |
| duodenal ulcer | 3 (0.1) | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| duodenal ulcer reactivated | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| duodenal ulcer scar | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| duodenitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| duodenum postbulbar ulcer | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| early gastric carcinoma | 6 (0.2) | 8 (0.5) | 5 (0.5) | 8 (0.5) |
| esophageal erosion | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| esophageal hiatal hernia | 64 (1.9) | 62 (3.9) | 28 (2.5) | 62 (4.0) |
| esophageal ulcer | 24 (0.7) | 10 (0.6) | 4 (0.4) | 10 (0.6) |
| esophageal varices associated with primary biliary cholangitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| esophageal varices hemorrhage associated with alcoholic cirrhosis | 3 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| esophageal varix associated with alcoholic cirrhosis | 7 (0.2) | 3 (0.2) | 6 (0.5) | 3 (0.2) |
| esophageal varix associated with cirrhosis | 11 (0.3) | 2 (0.1) | 5 (0.5) | 2 (0.1) |
| gastric MALT lymphoma | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| gastric antral carcinoma | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| gastric bleeding | 10 (0.3) | 7 (0.4) | 11 (1.0) | 7 (0.4) |
| gastric body cancer | 2 (0.1) | 3 (0.2) | 0 (0.0) | 3 (0.2) |
| gastric gastrointestinal stromal tumor | 1 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| gastric perforation | 14 (0.4) | 1 (0.1) | 3 (0.3) | 1 (0.1) |
| gastric ulcer | 3 (0.1) | 2 (0.1) | 2 (0.2) | 2 (0.1) |
| gastric ulcer perforation | 4 (0.1) | 2 (0.1) | 1 (0.1) | 2 (0.1) |
| gastroduodenal ulcer | 4 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| gastroesophageal reflux disease | 2 (0.1) | 2 (0.1) | 1 (0.1) | 2 (0.1) |
| gastrointestinal bleeding | 50 (1.5) | 25 (1.6) | 16 (1.4) | 25 (1.6) |
| gastropyloric cancer | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| hematemesis and melena | 14 (0.4) | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| hemorrhagic duodenal ulcer | 97 (2.9) | 19 (1.2) | 10 (0.9) | 19 (1.2) |
| hemorrhagic duodenal ulcer perforation | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| hemorrhagic gastric ulcer | 189 (5.7) | 44 (2.8) | 27 (2.4) | 44 (2.8) |
| hemorrhagic gastric ulcer perforation | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| hemorrhagic gastritis | 6 (0.2) | 2 (0.1) | 2 (0.2) | 2 (0.1) |
| hepatitis C virus-related decompensated liver cirrhosis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| idiopathic interstitial pneumonia | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| intestinal hemorrhage | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| intractable gastric ulcer | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.2) |
| intractable regurgitant esophagitis | 3 (0.1) | 3 (0.2) | 1 (0.1) | 3 (0.2) |
| large bowel cancer | 1 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| liver cirrhosis | 4 (0.1) | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| lower gastrointestinal hemorrhage | 17 (0.5) | 14 (0.9) | 8 (0.7) | 14 (0.9) |
| malignant lymphoma | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| middle esophageal cancer | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| mitral insufficiency and tricuspid insufficiency | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| mitral regurgitation | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| mitral valve incompetence | 1 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| morbid obesity | 27 (0.8) | 8 (0.5) | 6 (0.5) | 8 (0.5) |
| multiple duodenal ulcer | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| multiple gastric ulcer | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| multiple hemorrhagic gastric ulcer | 4 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| obesity | 5 (0.2) | 2 (0.1) | 7 (0.6) | 2 (0.1) |
| pancreatic carcinoma | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| paroxysmal atrial fibrillation | 1 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| penetrating duodenal ulcer | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| perforative duodenal ulcer | 27 (0.8) | 0 (0.0) | 4 (0.4) | 0 (0.0) |
| postoperative gastric ulcer | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| primary biliary cirrhosis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| prostate cancer | 1 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| pyloric antrum cancer | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.2) |
| reflux esophagitis | 16 (0.5) | 9 (0.6) | 7 (0.6) | 9 (0.6) |
| refractory reflux esophagitis requiring maintenance therapy | 1 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| residual stomach ulcer | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| severe ulcerative colitis | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| small intestinal bleeding | 2 (0.1) | 5 (0.3) | 2 (0.2) | 5 (0.3) |
| stomach cancer | 10 (0.3) | 9 (0.6) | 2 (0.2) | 9 (0.6) |
| stomach erosion | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| stomal ulcer | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ulcerative colitis–pancolitis type | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| ulcerative colitis–proctitis type | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| upper gastrointestinal hemorrhage | 268 (8.0) | 98 (6.2) | 63 (5.7) | 98 (6.3) |

MALT: mucosa-associated lymphoid tissue

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 4 weeks | | | 8 weeks | | | 6 months | | |
|  | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) |
| GERD-related cost |  |  |  |  |  |  |  |  |  |
| Therapeutic agents cost | 3037 | 5752 | −2717 (−2739.9 to −2691.5) | 4260 | 8172 | −3913 (−3948.2 to 3877.7) | 8516 | 16137 | −7620 (−7747.9 to −7532.5) |
| Endoscopy or X-ray examination cost | 779 | 1027 | −250 (-273.7 to -230.4) | 881 | 1143 | −262 (-286.9 - -237.9) | 1073 | 1330 | −258 (−298.1 to −232.5) |
| Treatment cost for upper gastrointestinal bleeding | 17 | 20 | −2 (-7.8–2.8) | 21 | 24 | −3 (−9.0 to 3.0) | 32 | 34 | −2 (−12.7 to 8.3) |
| Endoscopic treatments cost | 5 | 1 | 4 (3.3–4.1) | 6 | 2 | 4 (3.6–4.5) | 7 | 2 | 5 (4.1–5.2) |
| Laparoscopic surgery cost | - | - | - | - | - | - | - | - | - |
| Hospitalization cost | 17634 | 3477 | 14193 (12766.0– 15566.3) | 21715 | 4436 | 17382 (15873.0– 18978.1) | 28117 | 6097 | 21999 (20158.7–24505.6) |
| Total cost | 21406 | 10249 | 11173 (9768.0 –12571.7) | 26795 | 13736 | 13175 (11653.5– 14768.6) | 37619 | 23542 | 14051 (12205.5–16600.0) |

Supplementary Table 3: Healthcare costs per patients (cumulative cost after index date) (PPI vs. P-CAB, matched cohort, controlled population, patients with reflux esophagitis)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 4 weeks | | | 8 weeks | | | 6 months | | |
|  | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) |
| GERD-related cost |  |  |  |  |  |  |  |  |  |
| Therapeutic agents cost | 3037 | 5752 | −2717 (−2739.9 to −2691.5) | 4260 | 8172 | −3913 (−3948.2 to 3877.7) | 8516 | 16137 | −7620 (−7747.9 to −7532.5) |
| Endoscopy or X-ray examination cost | 779 | 1027 | −250 (-273.7 to -230.4) | 881 | 1143 | −262 (-286.9 - -237.9) | 1073 | 1330 | −258 (−298.1 to −232.5) |
| Treatment cost for upper gastrointestinal bleeding | 17 | 20 | −2 (-7.8–2.8) | 21 | 24 | −3 (−9.0 to 3.0) | 32 | 34 | −2 (−12.7 to 8.3) |
| Endoscopic treatments cost | 5 | 1 | 4 (3.3–4.1) | 6 | 2 | 4 (3.6–4.5) | 7 | 2 | 5 (4.1–5.2) |
| Laparoscopic surgery cost | - | - | - | - | - | - | - | - | - |
| Hospitalization cost | 17634 | 3477 | 14193 (12766.0– 15566.3) | 21715 | 4436 | 17382 (15873.0– 18978.1) | 28117 | 6097 | 21999 (20158.7–24505.6) |
| Total cost | 21406 | 10249 | 11173 (9768.0 –12571.7) | 26795 | 13736 | 13175 (11653.5– 14768.6) | 37619 | 23542 | 14051 (12205.5–16600.0) |
|  | 12 months | | | 18 months | | | 24 months | | |
|  | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) |
| GERD-related cost |  |  |  |  |  |  |  |  |  |
| Therapeutic agents cost | 13569 | 25622 | −12061 (−12299.7 to 11873.1) | 18361 | 34572 | −16199 (−16493.5 to −15937.2) | 23036 | 43162 | −20112 (−20533.2 to −19768.6) |
| Endoscopy or X-ray examination cost | 1264 | 1548 | −282 (−331.9 to 257.8) | 1732 | 2071 | −339 (−393.3 to −291.1) | 2167 | 2566 | −397 (−459.2 to −341.8) |
| Treatment cost for upper gastrointestinal bleeding | 41 | 43 | −3 (−17.7 to 7.7) | 51 | 52 | −1 (−14.0 to 14.0) | 62 | 61 | 1 (−17.2 to 13.8) |
| Endoscopic treatments cost | 7 | 2 | 5 (4.6–5.9) | 8 | 3 | 6 (4.9–6.4) | 10 | 3 | 6 (5.3–7.1) |
| Laparoscopic surgery cost | - | - | - | 67 | 58 | 8 (−51.1 to 49.7) | 113 | 113 | 1 (−78.6 to 53.8) |
| Hospitalization cost | 31467 | 6874 | 24618 (22434.6–27210.4) | 36840 | 9701 | 26771 (24605.0–30379.8) | 41717 | 13931 | 27500 (24384.1–32639.8) |
| Total cost | 46249 | 34019 | 12251 (9916.0–14692.1) | 56864 | 46376 | 10206 (7970.6–13759.2) | 66828 | 59713 | 6984 (3703.7–12025.5) |
|  | 36 months | | |
|  | PPI (N=151541) | P-CAB (N=151541) | Difference (95% CI) |
| GERD-related cost |  |  |  |
| Therapeutic agents cost | 32355 | 60297 | −27957 (−28635.6 to −27307.3) |
| Endoscopy or X-ray examination cost | 3068 | 3620 | −552 (−672.6 to −445.7) |
| Treatment cost for upper gastrointestinal bleeding | 89 | 75 | 14 (−11.4 to 34.4) |
| Endoscopic treatments cost | 12 | 5 | 7 (5.3–7.8) |
| Laparoscopic surgery cost | 222 | 218 | 3 (−106.2 to 107.0) |
| Hospitalization cost | 51260 | 20686 | 30272 (25445.4–36613.9) |
| Total cost | 86543 | 84512 | 1697 (−2936.5 to 8122.0) |

Supplementary Table 4: Healthcare costs per patients (cumulative cost after index date) (EPZ vs. P-CAB, matched cohort, controlled population, patients with reflux esophagitis)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 4 weeks | | | 8 weeks | | | 6 months | | |
|  | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) |
| GERD-related cost |  |  |  |  |  |  |  |  |  |
| Therapeutic agents cost | 4412 | 5753 | −1342 (−1364.0 to −1314.6) | 6212 | 8171 | −1961 (−1998.4 to−1917.9) | 12420 | 16139 | −3705 (−3833.1 to −3589.3) |
| Endoscopy or X-ray examination cost | 834 | 1031 | −196 (−223.3 to −177.2) | 946 | 1146 | −200 (−233.6 to −178.9) | 1128 | 1336 | −207 (−248.5 to −179.6) |
| Treatment cost for upper gastrointestinal bleeding | 11 | 19 | −9 (−12.2 to −5.7) | 14 | 24 | −9 (−14.2 to −5.3) | 23 | 34 | −11 (−18.6 to −5.5) |
| Endoscopic treatments cost | 1 | 1 | 0 (−0.5 to 0.1) | 1 | 2 | 0 (−0.4 to 0.2) | 2 | 2 | 0 (−0.4 to 0.4) |
| Laparoscopic surgery cost | - | - | - | - | - | - | - | - | - |
| Hospitalization cost | 3473 | 3573 | −39 (−843.8 to 719.8) | 4652 | 4560 | 171 (−897.8 to 1144.1) | 7486 | 6183 | 1365 (−487.5 to 3017.2) |
| Total cost | 8722 | 10349 | −1584 (−2385.7 to −810.6) | 11818 | 13858 | −1982 (−3051.1 to −1029.1) | 21041 | 23669 | −2540 (−4415.1 to −860.4) |
|  | 12 months | | | 18 months | | | 24 months | | |
|  | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) |
| GERD-related cost |  |  |  |  |  |  |  |  |  |
| Therapeutic agents cost | 19774 | 25619 | −5839 (−6020.4 to −5632.0) | 26658 | 34547 | −7890 (−8316.3 to −7556.2) | 33276 | 43134 | −9884 (−10467.4 to −9415.5) |
| Endoscopy or X-ray examination cost | 1343 | 1548 | −208 (−241.9 to −162.9) | 1842 | 2082 | −239 (−290.8 to −191.2) | 2262 | 2570 | −313 (−395.2 to −234.0) |
| Treatment cost for upper gastrointestinal bleeding | 30 | 43 | −13 (−25.2 to −5.2) | 40 | 51 | −12 (−23.1 to −1.9) | 53 | 61 | −8 (−20.4 to 3.1) |
| Endoscopic treatments cost | 2 | 2 | 0 (−0.4 to 0.6) | 3 | 3 | 0 (−0.2 to 0.8) | 4 | 3 | 0 (−0.4 to 1.0) |
| Laparoscopic surgery cost | - | - | - | 39 | 54 | −16 (−55.8 to 18.4) | 57 | 108 | −51 (−100.6 to −8.5) |
| Hospitalization cost | 9314 | 6867 | 2581 (643.4–4392.9) | 12121 | 10009 | 2164 (176.4 to 4716.6) | 14983 | 14015 | 813 (−2354.9 to 4079.4) |
| Total cost | 30414 | 34019 | −3616 (−5412.6 to −1594.4) | 40524 | 46536 | −6009 (−7988.2 to −3332.3) | 50450 | 59680 | −9307 (−12725.6 to −5793.9) |
|  | 36 months | | |
|  | esomeprazole (N=151355) | P-CAB (N=151355) | Difference (95% CI) |
| GERD-related cost |  |  |  |
| Therapeutic agents cost | 46248 | 60316 | −14031 (−15160.8 to −13307.6) |
| Endoscopy or X-ray examination cost | 3188 | 3631 | −449 (−542.4 to −336.0) |
| Treatment cost for upper gastrointestinal bleeding | 78 | 75 | 4 (−18.3 to 19.7) |
| Endoscopic treatments cost | 5 | 5 | 0 (−0.6 to 1.1) |
| Laparoscopic surgery cost | 155 | 218 | −62 (−175.5 to 5.6) |
| Hospitalization cost | 21974 | 20419 | 1750 (−3835.9 to 5460.3) |
| Total cost | 71223 | 84212 | −12811 (−18334.2 to −8836.4) |

Supplementary Table 5: Switching rate during hospitalization from branded to generic medication (matched cohort, overall population, patients with reflux esophagitis)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | PPI | P-CAB | esomeprazole | P-CAB |
| Number of hospitalization after index date | | 2723 (81.7) | 1208 (76.8) | 935 (84.3) | 1203 (76.7) |
|  | generic PPI switched from branded PPI or P-CAB | 307 (11.3) | 326 (27.0) | 392 (41.9) | 324 (26.9) |

Supplementary Table 6: Incidence rate of severe GERD-related complication (matched cohort, overall population, patients with reflux esophagitis)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PPI | index date | 4 weeks | 8weeks | 6 months | 12 months | 18months |
| Number of at risk | 242102 | 196749 | 181665 | 149483 | 119916 | 96251 |
| Number of event\* | 2005 | 4935 | 5441 | 6353 | 6993 | 7401 |
| incidence rate (95% CI) | 0.8 (0.79–0.87) | 2.2 (2.13–2.25) | 2.5 (2.39–2.52) | 3.0 (2.92 - 3.06) | 3.5 (3.37–3.53) | 3.8 (3.73–3.91) |
| P-CAB | index date | 4 weeks | 8weeks | 6 months | 12 months | 18months |
| Number of at risk | 242102 | 188460 | 171260 | 133819 | 99785 | 72464 |
| Number of event\* | 791 | 2961 | 3472 | 4202 | 4669 | 4975 |
| incidence rate (95% CI) | 0.3 (0.30–0.35) | 1.4 (1.33–1.43) | 1.7 (1.61–1.72) | 2.1 (2.06–2.19) | 2.5 (2.45 - 2.59) | 2.9 (2.79–2.95) |
| PPI | 24 months | 36 months | ALL |
| Number of at risk | 76757 | 46651 | 0 |
| Number of event\* | 7702 | 8115 | 8483 |
| incidence rate (95% CI) | 4.2 (4.06–4.25) | 4.8 (4.69–4.91) | 6.8 (6.32–7.24) |
| P-CAB | 24 months | 36 months | ALL |
| Number of at risk | 51175 | 22260 | 0 |
| Number of event\* | 5176 | 5408 | 5518 |
| incidence rate (95% CI) | 3.2 (3.10–3.28) | 3.8 (3.69–3.94) | 5.1 (4.74–5.57) |

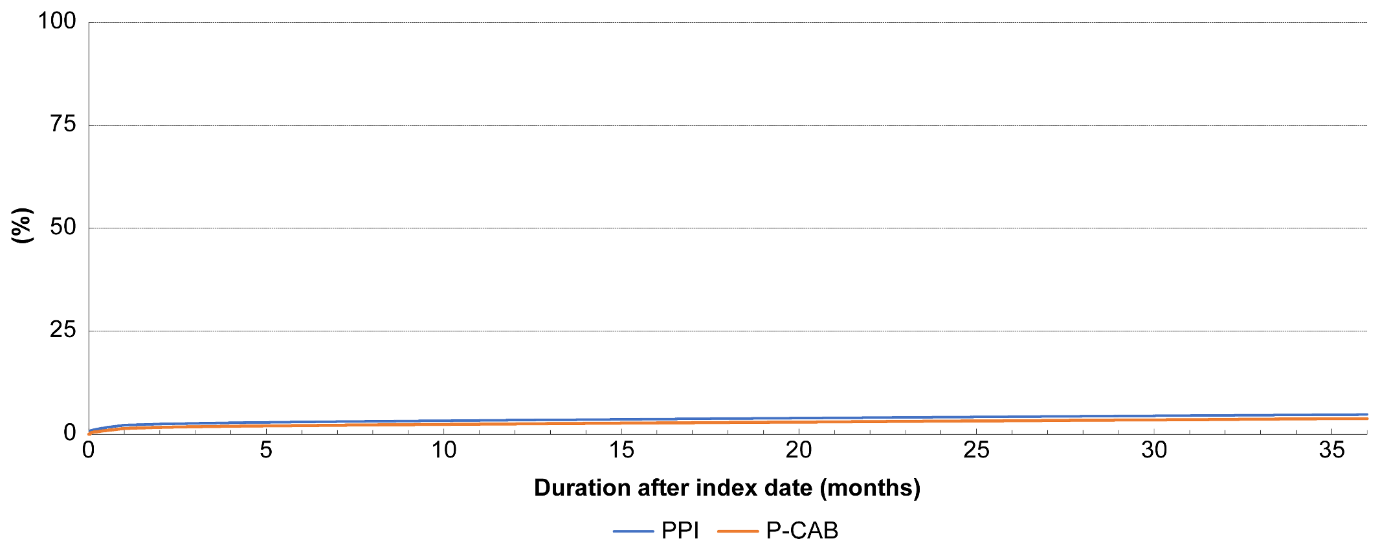
\*First occurrence of Severe GERD-related complication, which was defined as upper gastrointestinal bleeding or esophageal or gastroduodenal surgery and endoscopic treatment during follow-up period.



Supplementary Figure 1A. Disposition of patients with gastroesophageal reflux disease GERD (proton pump inhibitor [PPI] vs. potassium-competitive acid blocker [P-CAB])



Supplementary Figure 1B. Disposition of patients with gastroesophageal reflux disease (GERD) (esomeprazole [EPZ] vs. potassium-competitive acid blocker [P-CAB])



Supplementary Figure 2. Cumulative occurrence of severe gastroesophageal reflux disease (GERD)-related complication (proton pump inhibitor (PPI) vs. potassium-competitive acid blocker (P-CAB), matched cohort, overall population, patients with reflux esophagitis). Severe GERD-related complication was defined as upper gastrointestinal bleeding or esophageal or gastroduodenal surgery and endoscopic treatment during follow-up period. The first occurrence of severe GERD-related complication was treated as an event. Patients without severe GERD-related complication were censored at the date of last available record in the database.