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# Comparison of hepatotoxicity of tegoprazan, a novel potassium-competitive acid blocker, with proton pump inhibitors using real-world data: A nationwide cohort study

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**Background:** Proton pump inhibitors (PPIs) are acid suppressants that are frequently prescribed in many countries to reduce heartburn. A potassium-competitive acid blocker (P-CAB; tegoprazan) was launched relatively recently that also inhibits gastric acid secretion. This study aimed to compare the hepatotoxicity of the six existing PPIs with P-CAB.

**Methods:** This retrospective cohort study was conducted between January 2019 and December 2020 and included data from the total population of 50 million inhabitants in Korea. Propensity score (PS) matching was performed using 10 variables, and the differences in hepatotoxicity between P-CAB and the six PPIs were compared in a similar distribution. The primary endpoint was hepatotoxicity which included toxic liver disease, hepatitis, hepatic failure, liver transplantation, and other liver diseases.

**Results:** The risk ratios (RR) of tegoprazan vs. the six PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) were all significant [RR: 0.70 (95% CI: 0.69–0.72), 0.81 (95% CI: 0.79–0.83), 0.61 (95% CI: 0.59–0.63), 1.17 (95% CI: 1.13–1.20), 0.61 (95% CI: 0.59–0.62), and 0.73 (95% CI: 0.71–0.75), respectively]. The risk ratio of tegoprazan vs. the six existing PPIs was 0.73 (95% CI: 0.72–0.75). The hazard ratios (HRs) of hepatotoxicity of the six PPIs to tegoprazan showed significantly higher values apart from omeprazole (HR: dexlansoprazole, 1.13; esomeprazole, 1.04; lansoprazole, 1.25; omeprazole, 0.77; pantoprazole, 1.26; rabeprazole, 1.15, respectively, and the six existing PPIs, 1.10).

**Conclusion:** Using a large-scale data cohort analysis consisting of 50 million Koreans, tegoprazan did not induce higher hepatotoxicity compared with the six conventional PPIs.

KEYWORDS

P-CAB, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, PPI

# Introduction

Proton pump inhibitors (PPIs) are drugs that are frequently used to treat the symptoms associated with excessive gastric acid secretion. PPI is a treatment of choice drug to treat erosive esophagitis, GERD, and peptic ulcer disease and is an essential drug to increase the susceptibility of antibiotics in Helicobacter pylori eradication therapy (1-3). PPI has extensive Food and Drug Administration-approved indications such as (1) healing of erosive esophagitis, (2) maintenance of healed erosive esophagitis, (3) treatment of GERD, (4) risk reduction for gastric ulcer associated with NSAIDs, (5) H. pylori eradication to reduce the risk of duodenal ulcer recurrence in combination with antibiotics, (6) hypersecretory conditions including Zollinger-Ellison syndrome, and (7) short-term and maintenance treatment for duodenal ulcer (3). They irreversibly act as a disulfide bond to H<sup>+</sup>/K<sup>+</sup> ATPase resulting in a strong gastric acid inhibitory effect.

Despite a long history of use and relatively well-established safety profiles, PPIs still cannot completely fulfill the requirements necessary to control gastrointestinal (GI) problems. PPIs are inactive when taken and do not take effect until they are absorbed from the small intestine (4). To counter these limitations, potassium-competitive acid blockers (P-CABs) were developed in the early 1980s, and these bind reversibly to the K<sup>+</sup> binding domain of H<sup>+</sup>/K<sup>+</sup> ATPase to prevent gastric acid secretion. However, earlier P-CABs, such as SCH28080, were discontinued due to hepatotoxicity in the human study (5, 6). A phase 2 clinical trial of YH4808 for reflux esophagitis was discontinued due to hepatotoxicity (7). AZD0865, which was introduced to treat erosive and nonerosive reflux disease, had liver toxicity issues in a randomized comparative trial, and its development was discontinued (8, 9).

Currently, there are only three P-CABs (revaprazan, vonoprazan, and tegoprazan) that have overcome these problems and have been approved by some regulatory agencies (10). In South Korea, tegoprazan has been on the market since 2019. Although there were no significant side effects in phase 3 clinical trials of tegoprazan, the concerns over hepatotoxicity were not completely dispelled (11). Dyspepsia, chest discomfort, and headache are all reported as drug-related, treatment-emergent adverse events for tegoprazan, but the fact that it belongs to the P-CAB drug group does not completely eliminate the concern over hepatotoxicity that existed in early P-CABs.

Recently, many studies have been conducted using real-world data (RWD), including electronic health records and insurance claims data, for postmarket drug safety monitoring. Since South Korea has a national insurance system, the Health Insurance Review and Assessment (HIRA) Service, it is possible to evaluate the rare adverse drug reactions using the HIRA database. This study aimed to compare the risk of hepatotoxicity with tegoprazan vs. PPIs.

### **Methods**

#### Data source

Data selected from the anonymized HIRA database included patient demographics and detailed data from diagnosis. Since 99% of patients in Korea are enrolled in health insurance, the HIRA database is a dataset that is representative of the entire population. The database contains demographic data such as age, sex, and income quintile of all patients, and also medical information such as date of treatment, whether or not surgery was performed, outpatient or admitted as an inpatient, course of treatment, treatment details, diagnosis, and type of surgery.

#### Study design

This nationwide population-based retrospective cohort study compared the risk of hepatotoxicity from tegoprazan compared with PPIs.

#### Study population

The definition of the experimental cohort was "tegoprazan prescription". The definition of the comparable cohort was "any PPI prescription". The observation period was defined as the time from the first prescription of tegoprazan or PPI to the last day of tegoprazan or PPI plus up to 14 days. The inclusion criteria were as follows: (1) any tegoprazan or PPI drug user; and (2) age over 18 years. There were two exclusion criteria: (1) no follow-up data available in the database after the first prescription of tegoprazan or PPI; and (2) the patient taking two or more drugs among tegoprazan and six PPIs during the observation period. In the case of consecutive prescription dates in one patient, this case was evaluated as one case, and if prescriptions were received 28 days after the date of an earlier prescription, each was evaluated as a separate case.

#### Propensity score matching

In this study, 10 variables that may affect hepatotoxicity were defined as follows (12, 13). Demography: (1) age (per 10-year increase; reference age was set as the average age of all patients); (2) sex (reference: male); (3) antibiotic usage, and (4) seven liver-related diagnostic records <1 year before PPI or P-CAB prescription



(viral hepatitis, any type of malignancy, alcoholic hepatitis, chronic hepatitis, chronic hepatic failure, liver cirrhosis, and non-alcoholic fatty liver). To rule out hepatotoxicity from combined drugs, we used the combined antibiotics usage as matching variables in the propensity score matching. The antibiotics used are listed in Supplementary Table S1.

The independent variables in the comparable cohort had a distribution as similar as possible to the independent variables in the experimental cohort, and this was an essential part of the scientific method. For this purpose, 1:1 propensity score matching was performed six times (for P-CAB vs. the six PPIs) in the entire population. The propensity score was defined through logistic regression with 10 variables, and it was matched using the nearest greedy method. The potential risk of hepatotoxicity in the P-CAB and the PPI groups was equalized through propensity score matching.

#### Outcomes

The primary outcome was hepatotoxicity. Overall hepatotoxicity was subdivided on the basis of hepatotoxicity-related outcomes: (1) toxic liver disease; International Classification of Diseases, 10th revision (ICD-10), code K71; (2) hepatic failure, code K72; (3) hepatitis, codes K75.2, K75.9; (4) liver transplantation, code Z94.4; and (5) other liver diseases, codes K76, K76.2, K76.7, and K76.9. Any hepatotoxicity was defined as a new entry of an ICD-10 code for hepatotoxic disease during the observation period.

## Statistical analysis

Data analysis was conducted between January 2019 and December 2020. The Cox proportional hazard model was used considering the prescription day of tegoprazan or PPIs and the observation period. The hazard ratio (HR), risk ratio (RR), and cumulative incidence rate were calculated using R 3.5.3 software (R Foundation for Statistical Computing, Vienna, Austria).

# Results

# Baseline characteristics and incidence rates for hepatotoxicity with the six PPIs or tegoprazan

Among the 50 million people included in the HIRA database, 6,487,583 cases were defined in the study population (dexlansoprazole, 295,002; esomeprazole, 2,580,212; lansoprazole, 802,779; omeprazole, 251,966; pantoprazole, 675,991; rabeprazole, 1,352,744; and tegoprazan, 528,889) (Figure 1).

Considering the 10 variables, 1:1 propensity score matching was performed, and 1,737,176 out of 6,487,583 cases were selected as data to be used for analysis.

The standardized mean difference (SMD) values for the six PPI groups and the tegoprazan group for age, sex, use of antibiotics, and the seven liver-related underlying diseases were all <0.2, indicating a homogeneous distribution (Table 1). In South Korea, only one tablet per day is recognized in health insurance claims for all PPIs and P-CAB; therefore, all doses are the same with one tablet per day. The duration of prescription with regard to the six PPIs and P-CAB was not different, and the SMDs were <0.2; thus, it can be seen that there was relatively no significant difference in the dose and duration of prescription for P-CAB and the six PPIs (14, 15).

# Cumulative incidence rates of the six PPIs and tegoprazan

Tegoprazan had a lower cumulative incidence rate for overall hepatotoxicity than the six PPIs (Figure 2A). Subgroup analysis showed that tegoprazan clearly had a lower cumulative incidence rate than five of the PPIs (dexlansoprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) (Figure 2B).

# Risk ratios for hepatotoxicity of the six PPIs and tegoprazan

Tegoprazan had the lowest hepatotoxicity compared to the other PPIs. The risk ratio for tegoprazan vs. the six available PPIs was 0.73 (95% CI: 0.72–0.75) (Figure 3A). The risk ratios for tegoprazan vs. dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole were all significant [RR: 0.70 (95% CI: 0.69–0.72), 0.81 (95% CI: 0.79–0.83), 0.61

(95% CI: 0.59-0.63), 1.17 (95% CI: 1.13-1.20), 0.61 (95% CI: 0.59-0.62), and 0.73 (95% CI: 0.71-0.75), respectively] (Figure 3A).

In subgroup analysis, tegoprazan had a better result for RR [0.46 (95% CI: 0.31–0.68)] than omeprazole for liver transplantation, equivalent results for toxic liver disease and hepatic failure [RR; 1.01 (95% CI: 0.92–1.10), 0.52 (95% CI: 0.25–1.09), respectively], and a poorer outcome for acute hepatitis [RR; 1.42 (95% CI: 1.33–1.51)] (Figure 3B).

In all other subcategories, tegoprazan had lower RR values than the other five PPIs (Figure 3B).

## Cox proportional hazard analysis for hepatotoxicity of the six PPIs and tegoprazan

A Cox proportional hazard model was used to consider the interrelationships of all variables associated with hepatotoxicity over time. Apart from omeprazole, all PPIs had higher adjusted HRs for overall hepatotoxicity compared with tegoprazan [HR: 6 PPIs, 1.10 (95% CI: 1.08–1.13); dexlansoprazole, 1.13 (95% CI: 1.10–1.16); esomeprazole, 1.04 (95% CI: 1.01–1.07); lansoprazole, 1.25 (95% CI: 1.22–1.29); omeprazole, 0.77 (95% CI: 0.75–0.79); pantoprazole, 1.26 (95% CI: 1.23–1.29); and rabeprazole, 1.15 (95% CI: 1.12–1.18)] (Figure 4).

Overall, hepatotoxicity increased with age [HR 1.18 (95% CI: 1.17–1.19)], and there was a lower risk in women [HR 0.81 (95% CI: 0.80–0.82)].

Prior antibiotic use was a factor that increased the risk of hepatotoxicity [HR 1.31 (95% CI: 1.30–1.33)], and all seven liver-related underlying diseases (viral hepatitis, any type of malignancy, alcoholic hepatitis, chronic hepatitis, chronic hepatic failure, liver cirrhosis, and non-alcoholic fatty liver) were significant factors that increased hepatotoxicity [HR: 2.07 (95% CI: 2.03–2.12), 1.70 (95% CI: 1.67–1.73), 2.45 (95% CI: 2.37–2.52), 2.29 (95% CI: 2.23–2.34), 1.52 (95% CI: 1.27–1.82), 1.64 (95% CI: 1.56–1.73), 2.06 (95% CI: 2.02–2.10), respectively] (Figure 4).

## Discussion

Tegoprazan, a novel P-CAB that has recently been introduced, provides a good alternative for gastric acid-related problems (14). It is an acid-stable, rapid-acting, long-lasting, and reversible inhibitor of  $H^+$ - $K^+$  ATPase (7). We have shown that the hepatotoxicity of tegoprazan is significantly lower than the six available PPIs.

Proton pump inhibitors are known to be relatively safe since they have been used for peptic ulcer disease and *H. pylori* eradication for the past 30 years (15). However, there are reports that they affect calcium metabolism during long-term use and

	Tegoprazan	Dexlansoprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole	SMD
N (%)	248,168	248,168	248,168	248,168	248,168	248,168	248,168	
Age, years [mean (SD)]	52.96 (16.55)	56.14 (16.73)	55.19 (16.23)	56.86 (16.86)	53.55 (16.70)	56.81 (16.78)	56.11 (16.25)	0.09
Sex female	134,092 (54.03)	130,116 (52.43)	130,157 (52.45)	126,928 (51.15)	128,774 (51.89)	125,366 (50.52)	132,949 (53.57)	0.03
Sex male	114,076 (45.97)	118,052 (47.57)	118,011 (47.55)	121,240 (48.85)	119,394 (48.11)	122,802 (49.48)	115,219 (46.43)	
Antibiotic	150,376 (60.59)	160,523 (64.68)	157,546 (63.48)	162,199 (65.36)	145,699 (58.71)	157,028 (63.27)	156,247 (62.96)	0.06
Viral hepatitis	7,590 (3.06)	9,244 (3.72)	8,939 (3.60)	10,078 (4.06)	7,530 (3.03)	10,859 (4.38)	8,832 (3.56)	0.03
Malignancy	17,233 (6.94)	29,371 (11.84)	21,622 (8.71)	31,620 (12.74)	18,453 (7.44)	30,466 (12.28)	19,626 (7.91)	0.08
Alcoholic hepatitis	3,015 (1.21)	3,589 (1.45)	3,808 (1.53)	4,800 (1.93)	3,004 (1.21)	4,712 (1.90)	3,894 (1.57)	0.03
Chronic hepatitis	6,102 (2.46)	6,362 (2.56)	7,432 (2.99)	8,411 (3.39)	6,910 (2.78)	8,584 (3.46)	6,899 (2.78)	0.03
Chronic hepatic failure	27 (0.01)	38 (0.02)	61 (0.02)	75 (0.03)	41 (0.02)	97 (0.04)	42 (0.02)	0.09
Liver cirrhosis	652 (0.26)	916 (0.37)	1,066 (0.43)	1,169 (0.47)	637 (0.26)	1,396 (0.56)	1,048 (0.42)	0.02
Non-alcoholic fatty liver	13,439 (5.42)	12,670 (5.11)	13,728 (5.53)	13,251 (5.34)	13,771 (5.55)	13,402 (5.40)	15,014 (6.05)	0.01
Duration, days [mean (SD)]	32.21 (63.00)	67.37 (135.21)	53.25 (113.77)	68.26 (140.74)	45.42 (102.21)	68.53 (143.66)	58.40 (125.89)	0.14
Hepatotoxicity	9,169 (3.69)	13,011 (5.24)	11,364 (4.58)	15,034 (6.06)	7,866 (3.17)	15,103 (6.09)	12,570 (5.07)	0.06
Toxic liver disease	987 (0.40)	1,741 (0.70)	1,298 (0.52)	2,215 (0.89)	978 (0.39)	1,945 (0.78)	1,262 (0.51)	
Hepatic failure	11 (0.00)	21 (0.01)	52 (0.02)	54 (0.02)	21 (0.01)	55 (0.02)	22 (0.01)	
Acute hepatitis	2,285 (0.92)	3,311 (1.33)	2,558 (1.03)	2,941 (1.19)	1,609 (0.65)	3,127 (1.26)	2,966 (1.20)	
Liver transplantation	36 (0.01)	70 (0.03)	285 (0.11)	136 (0.05)	79 (0.03)	645 (0.26)	59 (0.02)	
Other liver disease	5,850 (2.36)	7,867 (3.17)	7,170 (2.89)	9,688 (3.90)	5,178 (2.09)	9,330 (3.76)	8,261 (3.33)	



cause an increased risk of hip fractures (16), and there are reports that they are associated with community-acquired pneumonia

(17). In addition, since all PPIs are metabolized by CYP2C19, the cytochrome P450 isozyme, there are reports stating that caution

Interaction     Total marker (P-CA)	•						
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Tragopozen vs Esonwande■BP710000.76 0.70 to 20)Tragopozen vs Esonwande■BP702000.101 (020 to 10)Tragopozen vs Robepozele■BP710200.276 0.72 to 20)Tragopozen vs Robepozele■BP710240.276 0.72 to 20)Tragopozen vs Robepozele■BP710240.276 0.72 to 20)Tragopozen vs Robenosztele■112250.226 0.05 to 20)Tragopozen vs Esonwande●111210.226 0.05 to 20)Tragopozen vs Esonwande●228510310.080 (0.95 to 20)Tragopozen vs Esonwande●228520110.276 0.06 to 20)Tragopozen vs Esonwande●228520110.276 0.06 to 20)Tragopozen vs Esonwande●228520110.276 0.06 to 20)Tragopozen vs Esonwande●1380.261 0.020Tragopozen vs Esonwande●1380.21 0.776 0.76 0.07 0.076 0.00 0.010Tragopozen vs Esonwande●1380.21 0.776 0.76 0.07 0.076 0.00 0.010Tragopozen vs Esonwande●1380.21 0.776 0.756 0.01 0.010T		Tegoprazan vs Dexlansoprazole		Hel	987	1742	0.57 (0.52 to 0.61)
Trapprotect vs Lansapratols     HI     B67     220     0.4.6 (0.4 1 to 0.4)       Tagoprotect vs Lansapratols     HI     B67     1002     0.5.0 (0.47 to 0.2)       Tagoprotect vs Pathapratols     HI     B67     1022     0.5.0 (0.47 to 0.2)       Tagoprotect vs Pathapratol     HI     B67     1024     0.5.2 (0.75 to 0.2)       Tagoprotect vs Definition     HI     11     225     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     11     226     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.52 (0.75 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.55 (0.25 to 0.2)       Tagoprotect vs Definition     HI     121     0.52 (0.75 to 0.2)     0.55 (0.25 to 0.2)		Tegoprazan vs Esomerazole		Hel	987	1300	0.76 (0.70 to 0.83)
Tragspresent vs Omegrazele#8679601.01 (0.82 to 1.0)Tragspresent vs Destencesorele8671.020.51 (0.77 to 0.5)Tragspresent vs Edestrezele8671.020.22 (0.16 to 0.5)Tragspresent vs Edestrezele112.250.22 (0.16 to 0.5)Tragspresent vs Edestrezele112.250.22 (0.16 to 0.5)Tragspresent vs Edestrezele112.250.22 (0.16 to 0.5)Tragspresent vs Edestrezele112.40.52 (0.25 to 1.0)Tragspresent vs Edestrezele112.50.22 (0.16 to 0.5)Tragspresent vs Edestrezele112.50.23 (0.16 to 0.5)Tragspresent vs Edestrezele112.50.23 (0.16 to 0.5)Tragspresent vs Edestrezele2.2552.650.65 (0.5 to 0.5)Tragspresent vs Edestrezele2.2552.610.50 (0.65 to 0.7)Tragspresent vs Edestrezele2.2552.610.72 (0.16 to 0.5)Tragspresent vs Edestrezele2.2552.610.72 (0.16 to 0.5)Tragspresent vs Edestrezele2.2552.610.72 (0.16 to 0.5)Tragspresent vs Edestrezele3.60.72 (0.16 to 0.5)Tragspresent vs Edestrezele3.60.72 (0.16 to 0.5)Tragspresent vs E		Tegoprazan vs Lansoprazole		н	987	2220	0.45 (0.41 to 0.48)
Tragsprazen vs Pentsprazele     iii     967     1962     0.51 (0.47 to 25)       Tragsprazen vs Bestsprazele     iii     967     1234     0.72 (0.72 to 25)       Tragsprazen vs Bestsmagnazele     iiii     11     225     0.22 (0.16 to 25)       Tragsprazen vs Bestsmagnazele     iiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii		Tegoprazan vs Omeprazole		Hei	987	980	1.01 (0.92 to 1.10)
Tegopration vn Rukespratische     #     967     124     0.78 (0.72 to 0.8)       Heptic Failure     1     225     0.29 (0.18 to 0.5)       Tegopration vn Eisenmerazie     11     225     0.29 (0.18 to 0.5)       Tegopration vn Eisenmerazie     11     225     0.29 (0.11 to 0.3)       Tegopration vn Eisenmerazie     11     24     0.20 (0.11 to 0.3)       Tegopration vn Eisenmerazie     11     21     0.20 (0.11 to 0.3)       Tegopration vn Eisenmerazie     11     21     0.20 (0.11 to 0.3)       Tegopration vn Eisenmerazie     11     21     0.20 (0.11 to 0.3)       Tegopration vn Einensprazie     11     21     0.20 (0.11 to 0.3)       Tegopration vn Einensprazie     128     1950     0.20 (0.11 to 0.3)       Tegopration vn Einensprazie     128     2155     0.30 (0.26 to 0.3)       Tegopration vn Einensprazie     1285     1950     0.33 (0.78 to 0.8)       Tegopration vn Einensprazie     1285     1950     0.20 (0.16 to 0.3)       Tegopration vn Einensprazie     11     2285     1950     0.20 (0.10 to 0.3)       Tegopratin v		Tegoprazan vs Pantoprazole		Hel	987	1962	0.51 (0.47 to 0.55)
Hepster Failure   11   225   0.20 (0.06 0.05)     Tregoprazan vie Devinangenzole   11   21   0.20 (0.05 0.05)     Tregoprazan vie Devinangenzole   11   20   0.20 (0.05 0.05)     Tregoprazan vie Tregoprazan vie Tregoprazan vie Tregoprazan   0.20   0.20 (0.05 0.05)     Tregoprazan vie Tregoprazan vie Tregoprazan   0.20   0.20 (0.05 0.05)     Tregoprazan vie Tregoprazan vie Tregoprazan   0.20   0.20 (0.05 0.05)     Tregoprazan vie Tregoprazan vie Tregoprazan   0.225   283   0.80 (0.05 0.05)     Tregoprazan vie Devinangenzole   225   281   0.27 (0.71 0.05 0.05)     Tregoprazan vie Devinangenzole   225   281   0.27 (0.71 0.05 0.05)     Tregoprazan vie Devinangenzole   225   281   0.27 (0.71 0.05 0.05)     Tregoprazan vie Devinangenzole   225   281   0.27 (0.71 0.05 0.05)     Tregoprazan vie Devinangenzole   2265   1261   0.27 (0.71 0.05 0.05)		Tegoprazan vs Rabeprazole		ю	987	1264	0.78 (0.72 to 0.85)
Tappprazin vs Derdamograzole   11   225   0.20 (0.16 to 0.51)     Tappprazin vs Derdamograzole   11   21   0.52 (0.25 to 1.09)     Tappprazin vs Derdamograzole   11   21   0.52 (0.25 to 1.09)     Tappprazin vs Derdamograzole   11   21   0.52 (0.25 to 1.09)     Tappprazin vs Derdamograzole   11   21   0.52 (0.25 to 1.09)     Tappprazin vs Derdamograzole   11   22   0.50 (0.24 to 1.03)     Tappprazin vs Derdamograzole   11   22   0.50 (0.24 to 1.03)     Tappprazin vs Derdamograzole   2255   1650   0.63 (0.78 to 0.87)     Tappprazin vs Derdamograzole   2255   2331   0.69 (0.64 to 0.82)     Tappprazin vs Derdamograzole   2255   247   0.76 (7.45 0.56)     Tappprazin vs Derdamograzole   2255   247   0.76 (7.45 0.26)		Hepatic Failure					
Tippprazan vs Edeamsopeazole   11   21   0.52 (0.25 to 1.09)     Tippprazan vs Esonewazole   11   52   0.21 (0.11 to 0.41)     Tippprazan vs Esonewazole   11   54   0.20 (0.11 to 0.39)     Tippprazan vs Esonewazole   11   55   0.20 (0.11 to 0.39)     Tippprazan vs Esonewazole   11   22   0.50 (0.25 to 1.09)     Tippprazan vs Esonewazole   11   22   0.50 (0.25 to 1.09)     Tippprazan vs Esonewazole   11   22   0.50 (0.25 to 1.09)     Tippprazan vs Esonewazole   11   22   0.50 (0.55 to .57)     Tippprazan vs Esonewazole   2285   3313   0.69 (0.65 to .57)     Tippprazan vs Esonewazole   2285   3154   0.73 (0.69 to .77)     Tippprazan vs Esonewazole   11   228   3154   0.73 (0.69 to .77)     Tippprazan vs Esonewazole   11   228   3154   0.73 (0.69 to .77)     Tippprazan vs Esonewazole   11   228   3154   0.73 (0.69 to .77)     Tippprazan vs Esonewazole   11   228   3154   0.73 (0.69 to .77)     Tippprazan vs Esonewazole   11   228   3161		Tegoprazan vs 6PPIs			11	225	0.29 (0.16 to 0.54)
Teoponzzan vs Ekonerazóle   +   11   52   0.21 0.11 to 0.41)     Teoponzzan vs Unesprazóle   +   11   54   0.20 (0.11 to 0.39)     Teoponzzan vs Unesprazóle   11   21   0.52 (0.25 to 1.29)     Teoponzzan vs Densprazóle   11   23   0.20 (0.11 to 0.39)     Teoponzzan vs Ekoperazóle   11   26   0.20 (0.11 to 0.39)     Teoponzzan vs Ekoperazóle   11   22   0.50 (0.25 to 1.53)     Teoponzzan vs Ekoperazóle   2255   1050   0.83 (0.79 to 0.87)     Teoponzzan vs Ebelencoprazóle   2285   2663   0.89 (0.84 to 0.87)     Teoponzzan vs Ebelencoprazóle   *   2285   2643   0.89 (0.74 to 0.82)     Teoponzzan vs Ebelencoprazóle   *   2285   3151   0.70 (0.82 to 0.77)     Teoponzzan vs Ebelencoprazóle   *   2285   3151   0.70 (0.82 to 0.77)     Teoponzzan vs Ebelencoprazóle   *   2285   3151   0.70 (0.82 to 0.77)     Teoponzzan vs Ebelencoprazóle   *   36   10.17 (0.12 to 0.24)     Teoponzzan vs Ebelencoprazóle   *   36   10.60 (0.01 to 0.8)     Teoponzzan vs Ebelencoprazóle		Tegoprazan vs Dexlansoprazole			11	21	0.52 (0.25 to 1.09)
Teoporazaru va Lensoprazole   11   44   0.20 (0.11 to 0.3)     Teoporazaru va Dentoprazole   11   21   0.52 (0.25 to 1.0)     Teoporazaru va Behoprazole   11   22   0.50 (0.24 to 1.0)     Acute Hoptatis   11   22   0.50 (0.24 to 0.3)     Teoporazaru va Behoprazole   *   2285   3131   0.69 (0.25 to 0.8)     Teoporazaru va Behoprazole   *   2285   3131   0.69 (0.26 to 0.7)     Teoporazaru va Destensoprazole   *   2285   3131   0.69 (0.26 to 0.7)     Teoporazaru va Destensoprazole   *   2285   3151   0.69 (0.8 to 0.8)     Teoporazaru va Dentensoprazole   *   2285   3151   0.79 (0.7 to 0.8)     Teoporazaru va Dentensoprazole   *   2285   3151   0.70 (0.7 to 0.8)     Teoporazaru va Dentensoprazole   *   2285   3151   0.70 (0.7 to 0.8)     Teoporazaru va Dentensoprazole   *   36   70   0.51 (0.3 to 0.4)     Teoporazaru va Dentensoprazole   *   36   70   0.51 (0.3 to 0.4)     Teoporazaru va Dentensoprazole   *   36   70   0.51 (0.3 to 0.6) </td <td></td> <td>Tegoprazan vs Esomerazole</td> <td><b>—</b>•</td> <td></td> <td>11</td> <td>52</td> <td>0.21 (0.11 to 0.41)</td>		Tegoprazan vs Esomerazole	<b>—</b> •		11	52	0.21 (0.11 to 0.41)
Tegoprizzan vs Omeprizzle   11   21   0.20 (0.21 to 0.39)     Tegoprizzan vs Rahoprizzle   11   22   0.50 (0.24 to 1.03)     Acute Hoptatis   11   22   0.50 (0.24 to 1.03)     Tegoprizzan vs Rahoprizzle   11   22   0.50 (0.24 to 0.37)     Tegoprizzan vs Esomerizzle   2285   3313   0.60 (0.65 to 0.7)     Tegoprizzan vs Esomerizzle   2285   263   0.60 (0.64 to 0.7)     Tegoprizzan vs Esomerizzle   2285   2641   0.74 (0.65 to 0.7)     Tegoprizzan vs Comprizzle   11   2285   0.61 (2   1.42 (3.15 (5))     Tegoprizzan vs Comprizzle   11   2285   2671   0.77 (0.71 to 0.21 (0.27 to 0.21)     Tegoprizzan vs Rahoprizzle   11   2285   2671   0.77 (0.71 to 0.21 (0.24)     Tegoprizzan vs Rahoprizzle   11   2285   2671   0.77 (0.71 to 0.21 (0.24)     Tegoprizzan vs Esomerizzle   11   2285   2671   0.77 (0.71 to 0.24)     Tegoprizzan vs Esomerizzle   11   286   138   0.77 (0.71 to 0.24)     Tegoprizzan vs Esomerizzle   11   286   138   0.27 (0.71 to 0.24) <td< td=""><td></td><td>Tegoprazan vs Lansoprazole</td><td><b></b></td><td>-</td><td>11</td><td>54</td><td>0.20 (0.11 to 0.39)</td></td<>		Tegoprazan vs Lansoprazole	<b></b>	-	11	54	0.20 (0.11 to 0.39)
Tegoprizzan vs Pantoprizzole   11   55   0.20 (0.11 to 0.3)     Acuto Heptatis   11   22   0.50 (0.24 to 1.0)     Acuto Heptatis   2285   16500   0.43 (0.79 to 0.87)     Tegoprizzan vs Econerazole   2285   2683   0.69 (0.64 to 0.8)     Tegoprizzan vs Econerazole   2285   2683   0.69 (0.64 to 0.8)     Tegoprizzan vs Econerazole   2285   2681   0.69 (0.64 to 0.8)     Tegoprizzan vs Econerazole   2285   2681   0.69 (0.64 to 0.8)     Tegoprizzan vs Econerazole   2285   2681   0.69 (0.64 to 0.8)     Tegoprizzan vs Econerazole   2285   2681   0.70 (0.74 to 0.8)     Tegoprizzan vs Econerazole   2285   2161   1.42 (1.33 to 1.51)     Tegoprizzan vs Rabeprizzole   2285   2161   0.70 (0.74 to 0.2)     Tegoprizzan vs Econerazole   2285   2161   0.70 (0.72 to 0.2)     Tegoprizzan vs Econerazole   4   268   2121   0.70 (0.72 to 0.2)     Tegoprizzan vs Econerazole   4   36   136   0.27 (0.15 to 0.2)     Tegoprizzan vs Econerazole   4   36   136   0.06 (0.04 to 0.6)		Tegoprazan vs Omeprazole	⊢		11	21	0.52 (0.25 to 1.09)
Tagoprazan vs Rabeprazole   1   2   5.0.0.0.24 to 1.0.0     Acuto Heptatis   2285   16560   0.83 (0.79 to 0.87)     Tegoprazan vs 6PPis   2285   3313   0.69 (0.65 to 0.73)     Tegoprazan vs Esomerazole   2285   2633   0.89 (0.64 to 0.04)     Tegoprazan vs Comeprazole   2285   2631   0.89 (0.64 to 0.04)     Tegoprazan vs Comeprazole   2285   2631   0.89 (0.64 to 0.04)     Tegoprazan vs Comeprazole   2285   2631   0.89 (0.64 to 0.04)     Tegoprazan vs Comeprazole   2285   2631   0.77 (0.70 to 0.80)     Tegoprazan vs Roheprazole   2285   2631   0.77 (0.70 to 0.80)     Tegoprazan vs Roheprazole   2285   2631   0.77 (0.70 to 0.80)     Tegoprazan vs Roheprazole   2285   2631   0.77 (0.70 to 0.20)     Tegoprazan vs Roheprazole   4   38   0.27 (0.12 to 0.24)     Tegoprazan vs Esomerazole   4   38   0.27 (0.18 to 0.30)     Tegoprazan vs Esomerazole   4   38   0.27 (0.18 to 0.30)     Tegoprazan vs Esomerazole   4   38   0.51 (0.44 to 0.09)     Tegoprazan vs Esomerazole		Tegoprazan vs Pantoprazole	<b>⊢</b> ●	-	11	55	0.20 (0.11 to 0.39)
Accord begintsin     12285     16500     0.83 (0.79 to 0.87)       Tegoprazan vs BPPis     2285     3313     0.69 (0.65 to 0.73)       Tegoprazan vs Esonerazole     2285     2663     0.89 (0.44 to 0.94)       Tegoprazan vs Esonerazole     2285     2447     0.78 (0.74 to 0.82)       Tegoprazan vs Omeprazole     111     2285     3154     0.70 (0.69 to 0.77)       Tegoprazan vs Omeprazole     111     2285     3154     0.70 (0.69 to 0.77)       Tegoprazan vs Babeprazole     112     0.77 (0.73 to 0.81)     0.77 (0.73 to 0.81)       Liver Taneplantation     112     0.77 (0.73 to 0.81)     0.77 (0.73 to 0.81)       Tegoprazan vs Bebrinsoprazole     114     38     70     0.51 (0.34 to 0.77)       Tegoprazan vs Bebrinsoprazole     114     38     79     0.46 (0.01 to 0.30)       Tegoprazan vs Bebrinsoprazole     114     38     79     0.46 (0.31 to 0.68)       Tegoprazan vs Bebrinsoprazole     114     38     79     0.46 (0.31 to 0.68)       Tegoprazan vs Bebrinsoprazole     115     115     0.66 (0.41 to 0.09)     0.66 (0.41 to 0.09)     0.66 (0.41		Tegoprazan vs Rabeprazole	<b></b>	•	11	22	0.50 (0.24 to 1.03)
Tegoprazan vs BPHs     2285     16560     0.83 (0.79 to 0.87)       Tegoprazan vs Dextansoprazole     2285     2333     0.69 (0.65 to 0.73)       Tegoprazan vs Exomerazole     2285     2593     0.89 (0.64 to 0.94)       Tegoprazan vs Dextansoprazole     2285     2947     0.76 (0.74 to 0.82)       Tegoprazan vs Dextansoprazole     2285     2947     0.76 (0.74 to 0.82)       Tegoprazan vs Dextansoprazole     2285     2947     0.77 (0.74 to 0.82)       Tegoprazan vs Rabeprazole     2285     2947     0.77 (0.73 to 0.81)       Liver Transplantation     2285     2971     0.77 (0.73 to 0.81)       Tegoprazan vs BPHs     186     1281     0.17 (0.12 to 0.24)       Tegoprazan vs Bevenerazole     196     38     70     0.51 (0.34 to 0.77)       Tegoprazan vs Bevenerazole     196     38     39     0.60 (0.04 to 0.08)       Tegoprazan vs Belonerazole     196     38     651     0.08 (0.04 to 0.08)       Tegoprazan vs Behoprazole     196     38     651     0.02 (0.04 to 0.08)       Tegoprazan vs Behoprazole     196     38     651		Acute Heptatis					
Tegoprazar vs Dexlansoprazole     ×     2285     3313     0.69 (0.65 to 0.7))       Tegoprazar vs Esomerazole     ×     2285     2663     0.89 (0.44 to 0.82)       Tegoprazar vs Lansoprazole     ×     2285     2447     0.76 (0.74 to 0.82)       Tegoprazar vs Cmeprazole     ×     2285     2447     0.76 (0.74 to 0.82)       Tegoprazar vs Cmeprazole     ×     2285     3154     0.73 (0.66 to 0.7)       Tegoprazar vs Pantoprazole     ×     2285     2971     0.77 (0.73 to 0.81)       Liver Transplantation     ×     2285     2971     0.77 (0.73 to 0.81)       Tegoprazar vs Esomerazole     ✓     36     1281     0.17 (0.12 to 0.24)       Tegoprazar vs Esomerazole     ✓     36     1281     0.017 (0.12 to 0.24)       Tegoprazar vs Esomerazole     ✓     36     136     0.31 (0.09 to 0.19)       Tegoprazar vs Esomerazole     ✓     36     136     0.66 (0.04 to 0.09)       Tegoprazar vs Esomerazole     ✓     36     59     0.61 (0.40 to 0.93)       Tegoprazar vs Bateprazole     ✓     36     59		Tegoprazan vs 6PPIs			2285	16560	0.83 (0.79 to 0.87)
Tegoprazar vs Esonerazole     2285     2563     0.89 (0.84 to 0.82)       Tegoprazar vs Esonerazole     2285     2947     0.76 (0.74 to 0.82)       Tegoprazar vs Omeprazole     2285     1612     1.42 (1.33 to 1.51)       Tegoprazar vs Pantoprazole     2285     3154     0.73 (0.69 to 0.77)       Tegoprazar vs Pantoprazole     2285     3154     0.73 (0.69 to 0.77)       Tegoprazar vs Pantoprazole     2285     2971     0.77 (0.73 to 0.81)       Liver Transplantation     1281     0.17 (0.12 to 0.24)     0.51 (0.34 to 0.77)       Tegoprazar vs Esonerazole     ↓ ↓ ↓     36     1281     0.17 (0.12 to 0.24)       Tegoprazar vs Esonerazole     ↓ ↓ ↓     36     2285     0.33 (0.09 to 0.19)       Tegoprazar vs Esonerazole     ↓ ↓ ↓     36     79     0.46 (0.31 to 0.89)       Tegoprazar vs Omeprazole     ↓ ↓ ↓     36     59     0.61 (0.40 to 0.89)       Tegoprazar vs Bateprazole     ↓ ↓ ↓     36     59     0.61 (0.40 to 0.89)       Tegoprazar vs Msebeprazole     ↓ ↓ ↓     36     59     0.61 (0.40 to 0.89)       Tegoprazar vs Bateprazole		Tegoprazan vs Dexlansoprazole		н	2285	3313	0.69 (0.65 to 0.73)
Tegoprazan vs Lansoprazole     #     2285     2947     0.78 (0.74 to 0.28)       Tegoprazan vs Omeprazole     #     2285     1612     1.42 (1.33 to 1.51)       Tegoprazan vs Dambprazole     #     2285     3154     0.73 (0.69 to 0.77)       Tegoprazan vs Dambprazole     #     2285     3154     0.73 (0.69 to 0.77)       Tegoprazan vs Babeprazole     #     2285     2971     0.77 (0.73 to 0.81)       Liver Transplantation     #     36     1281     0.17 (0.12 to 0.24)       Tegoprazan vs Eomerazole     #     36     1281     0.17 (0.12 to 0.24)       Tegoprazan vs Eomerazole     #     36     1281     0.17 (0.12 to 0.24)       Tegoprazan vs Eomerazole     #     36     1281     0.17 (0.12 to 0.24)       Tegoprazan vs Eomerazole     #     36     136     0.27 (0.18 to 0.38)       Tegoprazan vs Eomerazole     #     36     59     0.61 (0.40 to 0.69)       Tegoprazan vs Bateprazole     #     36     59     0.61 (0.40 to 0.69)       Tegoprazan vs Bateprazole     #     36     59     0.61		Tegoprazan vs Esomerazole		ы	2285	2563	0.89 (0.84 to 0.94)
Tegoprazan vs Omeprazole     Internet     Interne     Internet     Inter		Tegoprazan vs Lansoprazole			2285	2947	0.78 (0.74 to 0.82)
Tegoprazan vs Pantoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Pantoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Rabeprazole     Image: Section of the (1.000 0.00)       Liver Transplantation     Image: Section of the (1.000 0.00)       Tegoprazan vs BePlis     Image: Section of the (1.000 0.00)       Tegoprazan vs Beplis     Image: Section of the (1.000 0.00)       Tegoprazan vs Beplis     Image: Section of the (1.000 0.00)       Tegoprazan vs Beplis     Image: Section of the (1.000 0.00)       Tegoprazan vs Beplis     Image: Section of the (1.000 0.00)       Tegoprazan vs Beplis     Image: Section of the (1.000 0.00)       Tegoprazan vs Benerazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Esomerazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bentoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bentoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bettoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bettoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bettoprazole     Image: Section of the (1.000 0.00)       Tegoprazan vs Bettoprazole     Image: Section of the (1.000 0.00)       <		Tegoprazan vs Omenrazole		h	2285	1612	1.42 (1.33 to 1.51)
Tegoprazan vs Rabeprazole   ■   2285   2971   0.73 (0.58 0 0.77)     Liver Transplantation   -   36   1281   0.17 (0.73 to 0.81)     Tegoprazan vs BePlis   →   36   1281   0.17 (0.72 to 0.24)     Tegoprazan vs Berlansoprazole   →   36   286   0.13 (0.09 to 0.16)     Tegoprazan vs Exomerazole   →   36   286   0.13 (0.09 to 0.16)     Tegoprazan vs Lansoprazole   →   36   286   0.13 (0.09 to 0.16)     Tegoprazan vs Lansoprazole   →   36   286   0.13 (0.09 to 0.16)     Tegoprazan vs Lansoprazole   →   36   286   0.06 (0.04 to 0.39)     Tegoprazan vs Pantoprazole   →   36   651   0.06 (0.04 to 0.09)     Tegoprazan vs Bateprazole   →   36   59   0.61 (0.40 to 0.93)     Other liver disease   -   36   59   0.61 (0.40 to 0.69)     Tegoprazan vs Exomerazole   ■   5850   771   0.74 (0.72 to 0.7)     Tegoprazan vs Exomerazole   ■   5850   7184   0.82 (0.79 to 0.8)     Tegoprazan vs Exomerazole   ■   5850   7		Tegoprazan vs Pantoprazole			2285	3154	0.73 (0.69 to 0.77)
Liver Transplantation   36   1281   0.17 (0.12 to 30 0.01)     Liver Transplantation   38   1281   0.17 (0.12 to 30 0.01)     Tegoprazan vs GPPIs   4   36   70   0.51 (0.34 to 0.77)     Tegoprazan vs Esomerazole   4   36   286   0.13 (0.09 to 0.18)     Tegoprazan vs Lansoprazole   4   36   286   0.13 (0.09 to 0.18)     Tegoprazan vs Lansoprazole   4   36   286   0.13 (0.09 to 0.18)     Tegoprazan vs Comprazole   4   36   286   0.06 (0.04 to 0.08)     Tegoprazan vs Pantoprazole   4   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betheprazole   4   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betheprazole   4   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betheprazole   4   5850   7871   0.74 (0.72 to 0.70)     Tegoprazan vs Betheprazole   4   5850   7184   0.82 (0.79 to 0.84)     Tegoprazan vs Lansoprazole   4   5850   5188   1.13 (1.09 to 1.17)     Tegoprazan vs Comperazole   4   5850   5188   1.13 (1.		Tegoprazan vs Rabeprazole		int in the second se	2285	2971	0.77 (0.73 to 0.81)
Tegoprazan vs GPPIs   36   1281   0.17 (0.12 to 0.24)     Tegoprazan vs Dexlansoprazole   38   70   0.51 (0.34 to 0.77)     Tegoprazan vs Esomerazole   38   286   0.13 (0.09 to 0.18)     Tegoprazan vs Lansoprazole   36   138   0.27 (0.18 to 0.38)     Tegoprazan vs Dexlansoprazole   36   138   0.27 (0.18 to 0.38)     Tegoprazan vs Pantoprazole   36   79   0.46 (0.31 to 0.69)     Tegoprazan vs Pantoprazole   36   651   0.06 (0.04 to 0.09)     Tegoprazan vs Rateprazole   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betlansoprazole   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betlansoprazole   36   59   0.61 (0.40 to 0.93)     Tegoprazan vs Betlansoprazole   4   5850   7671   0.74 (0.72 to 0.7)     Tegoprazan vs Betlansoprazole   8850   7184   0.82 (0.79 to 0.8)   0.82 (0.79 to 0.8)     Tegoprazan vs Lansoprazole   8850   9709   0.60 (0.58 to 0.62)   1.13 (1.09 to 1.17)     Tegoprazan vs Pantoprazole   8850   5188   1.13 (1.09 to 1.17)     Tegoprazan vs Pantoprazole   8850		Liver Transplantation			2200		(3.70 (0 0.01)
Tegoprazan vs Dexlansoprazole Image: State of the sta		Tegoprazan vs 6PPIs	<b>—</b>		36	1281	0.17 (0.12 to 0.24)
Tegoprazan vs Esomerazole     Image: Constraint opticable     Image: Constraint opticable <thi< td=""><td></td><td>Tegoprazan vs Devlansonrazole</td><td></td><td></td><td>36</td><td>70</td><td>0.51 (0.34 to 0.77)</td></thi<>		Tegoprazan vs Devlansonrazole			36	70	0.51 (0.34 to 0.77)
Tegoprazan vs Lansoprazole Image: Construct of Constr		Tegoprazan ve Feomerazole			36	286	0.13 (0.09 to 0.18)
Tegoprazan vs Dentoprazole      36     153     0.1, 0.1, 0.1, 0.0, 0.3)       Tegoprazan vs Pantoprazole      36     79     0.46 (0.31 to 0.6.3)       Tegoprazan vs Pantoprazole      36     651     0.06 (0.04 to 0.06)       Tegoprazan vs Pantoprazole      36     59     0.61 (0.40 to 0.63)       Other liver disease      36     59     0.74 (0.72 to 0.76)       Tegoprazan vs Behlansoprazole      5850     7871     0.74 (0.72 to 0.76)       Tegoprazan vs Exomerazole      5850     7871     0.74 (0.72 to 0.76)       Tegoprazan vs Exomerazole      5850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole      5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Comprazole      5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole      5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole      5850     2275     0.71 (0.89 to 0.7)		Tegeprezen va Lansoprezelo			36	126	0.27 (0.18 to 0.28)
Tegoprazan vs Pantoprazole     33     79     0.48 (0.31 to 0.68)       Tegoprazan vs Pantoprazole     36     651     0.06 (0.04 to 0.08)       Tegoprazan vs Rabeprazole     36     59     0.61 (0.40 to 0.33)       Other liver disease     36     59     0.74 (0.72 to 0.76)       Tegoprazan vs Behlansoprazole     \$850     7671     0.74 (0.72 to 0.76)       Tegoprazan vs Esomerazole     \$850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     \$850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     \$850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Lansoprazole     \$850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     \$850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     \$850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     \$850     2275     0.71 (0.69 to 0.73)		Tegoprazan vs Cansoprazole			30	70	0.46 (0.31 to 0.58)
Tegoprazan vs Rabeprazole     36     661     0.06 (0.4 l0 0.08)       Tegoprazan vs Rabeprazole     36     59     0.61 (0.4 l0 0.08)       Other liver disease     36     59     0.61 (0.4 l0 0.08)       Tegoprazan vs GPPIs     5850     47637     0.74 (0.72 to 0.76)       Tegoprazan vs GPPIs     5850     7871     0.74 (0.72 to 0.77)       Tegoprazan vs Esomerazole     \$5850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     \$850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Uneprazole     \$850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     \$850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     \$850     8275     0.71 (0.89 to 0.73)		Tegopiazan vs Omepiazole			30	79	0.46 (0.31 to 0.68)
Tegopirazan va Arategorazole     36     59     061 (0.40 to 0.5)       Other liver disease     -     5850     47837     0.74 (0.72 to 0.76)       Tegopirazan va SeNansoprizzole     =     5850     7871     0.74 (0.72 to 0.77)       Tegopirazan vs Esomerazole     =     5850     7184     0.82 (0.79 to 0.84)       Tegopirazan vs Lansopirazole     =     5850     9709     0.60 (0.58 to 0.62)       Tegopirazan vs Uneprazole     =     5850     5188     1.13 (1.09 to 1.17)       Tegopirazan vs Pantoprazole     =     5850     9410     0.63 (0.61 to 0.65)       Tegopirazan vs Rabepirazole     =     5850     2275     0.71 (0.69 to 0.7)		Tegopiazan vs Pantopiazole			30	50	0.06 (0.04 to 0.08)
Tegoprazan vs 6PPis     5850     47637     0.74 (0.72 to 0.76)       Tegoprazan vs 0eklansoprazole     *     5850     7671     0.74 (0.72 to 0.77)       Tegoprazan vs Deklansoprazole     *     5850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     *     5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Dekprazole     *     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     *     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     *     5850     2275     0.71 (0.69 to 0.73)		other liver discourse			36	28	0.01 (0.40 to 0.93)
Iegoprazan vs br/ris     5850     47637     0.74 (0.72 to 0.76)       Tegoprazan vs Dexlansoprazole     #     5850     7871     0.74 (0.72 to 0.77)       Tegoprazan vs Dexlansoprazole     #     5850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     #     5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Omeprazole     #     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     8275     0.71 (0.69 to 0.73)		Other liver disease					
Tegoprazan vs Dexlansoprazole     #     5850     7871     0.74 (0.72 to 0.7)       Tegoprazan vs Esomerazole     #     5850     714     0.82 (0.79 to 0.8)       Tegoprazan vs Lansoprazole     #     5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Omeprazole     #     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     8275     0.71 (0.69 to 0.7)		Legoprazan vs 6PPIs		*	5850	47637	0.74 (0.72 to 0.76)
Tegoprazan vs Esomerazole     #     5850     7184     0.82 (0.79 to 0.84)       Tegoprazan vs Lansoprazole     #     5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Omeprazole     #     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     9410     0.63 (0.61 to 0.65)		Tegoprazan vs Dexlansoprazole		*	5850	7871	0.74 (0.72 to 0.77)
Tegoprazan vs Lansoprazole     #     5850     9709     0.60 (0.58 to 0.62)       Tegoprazan vs Omeprazole     #     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     8275     0.71 (0.69 to 0.73)		Tegoprazan vs Esomerazole		*	5850	7184	0.82 (0.79 to 0.84)
Tegoprazan vs Omeprazole     #     5850     5188     1.13 (1.09 to 1.17)       Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     8275     0.71 (0.69 to 0.73)		Tegoprazan vs Lansoprazole			5850	9709	0.60 (0.58 to 0.62)
Tegoprazan vs Pantoprazole     #     5850     9410     0.63 (0.61 to 0.65)       Tegoprazan vs Rabeprazole     #     5850     8275     0.71 (0.69 to 0.73)		Tegoprazan vs Omeprazole		*	5850	5188	1.13 (1.09 to 1.17)
Tegoprazan vs Rabeprazole 📕 5850 8275 0.71 (0.69 to 0.73)		Tegoprazan vs Pantoprazole		×	5850	9410	0.63 (0.61 to 0.65)
· · · · · · · · · · · · · · · · · · ·		Tegoprazan vs Rabeprazole		*	5850	8275	0.71 (0.69 to 0.73)

FIGURE 3

(A) Forest plots of overall hepatotoxicities showing the risk ratios for tegoprazan vs. the six available PPIs. (B) Forest plots of each hepatotoxicity in subgroup analysis showing the risk ratios for tegoprazan vs. the six available PPIs.



should be exercised when co-administered with drugs such as clopidogrel (15). Theoretically, since PPIs are metabolized in the liver, they may be hepatotoxic, and this was reported in several articles (18–20).

Tegoprazan is a novel drug that was approved in 2018 and launched in March 2019 in Korea. We evaluated its hepatotoxicity by analyzing the claims data from HIRA for a 1-year period after launch (January 2019 to December 2020). In South Korea, National Health Insurance covers  $\sim$ 98% of the total Korean population; thus, large-scale longitudinal cohort data analysis was possible.

In this study, hepatotoxicity was analyzed by dividing the patients into five subgroups (toxic liver disease, hepatic failure, hepatitis, liver transplantation, and other liver diseases) based on the hepatotoxicity-related outcome. We analyzed hepatotoxicity using various statistical models—the incidence rate, the cumulative incidence rate using the Cox proportional hazard model, and the risk ratio.

This study had several limitations. First, there is an inherent disadvantage embodied in the research design of a retrospective

study. Second, in the definition of hepatotoxicity, laboratory results or image tests were not included, and as it was a claimbased study, it was defined only by the ICD-10 code.

However, to overcome these disadvantages, we analyzed a large-scale dataset of  $\sim$ 250,000 individuals using propensity score matching, a technique that has only recently been introduced. It controlled tegoprazan and each PPI so that they had similar risks of hepatotoxicity. In addition, the strength of this study is that it identified the hepatotoxicity of PPI and P-CAB accurately by analyzing the entire population data of 50 million people in South Korea.

In conclusion, when analyzed using real data, tegoprazan did not induce higher hepatotoxicity compared to six conventional PPIs. Although the six existing PPIs are recognized as relatively safe drugs, in this study, tegoprazan was associated with lower hepatotoxicity than these PPIs. It reduced the risk of overall hepatotoxicity by  $\sim$ 27% compared with the PPIs. In the future, real-world data-based drug safety monitoring will be able to confirm the hepatotoxicity of tegoprazan more clearly.

### Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

### **Ethics statement**

This study protocol was reviewed and approved by the Institutional Review Board of JBNUH (IRB number CUH 2020-04-029-002). As information used for analyses from the NHIS-National Sample Cohort database was encrypted, anonymized, and de-identified, informed consent was not required.

# Author contributions

M-GK: conceptualization, writing—review and editing, and project administration. Y-JI, J-HL, E-YK, and SY: data curation and statistical analysis. JK: data curation, analysis and interpretation of data, and writing—original draft preparation. All authors contributed to the article and approved the submitted version.

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# **Conflict of interest**

M-GK is the CEO of Nanum Space Co. Ltd. Y-JI and E-YK are employed by Nanum Space Co. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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### Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fmed.2022.1076356/full#supplementary-material

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