Temporal trends in use of antisecretory agents among patients administered clopidogrel- based dual antiplatelet therapy after percutaneous coronary intervention

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Research Article

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Abstract

Background:

Antisecretory drugs are commonly prescribed with clopidogrel-based dual antiplatelet therapy (DAPT) to prevent gastrointestinal bleeding in high-risk patients after percutaneous coronary intervention (PCI). However, omeprazole and esomeprazole (inhibiting proton pump inhibitors [PPIs]) increase cardiovascular event rates on co-administration with clopidogrel.

This study aimed to examine trends in the use of antisecretory agents in patients administered clopidogrel-based DAPT and the concomitant use of clopidogrel and inhibiting PPIs.

Methods:

We used National Inpatient Sample data compiled by the Health Insurance Review & Assessment Service from 2009 to 2020. Further, we identified patients who were prescribed clopidogrel-based DAPT after PCI and investigated the concomitant use of antisecretory agents with clopidogrel. To verify the annual trend of drug utilization, we used the Cochran–Armitage trend test.

Results:

From 2009 to 2020, the percentage of H2 receptor antagonists users decreased steadily (from 82.5 % in 2009 to 25.3 % in 2020); instead, the percentage of PPI users increased (from 34.7 % in 2009 to 69.0 % in 2020). The use of inhibiting PPI also increased (from 4.2 % in 2009 to 30.7 % in 2020). P-CAB was rarely used before 2019; however, in 2020, it accounted for 7.8 % of the antisecretory users.

Conclusions:

Our study demonstrates that the use of inhibiting PPIs increased steadily in patients administered clopidogrel-based DAPT therapy. This is a major concern since the concomitant use of inhibiting PPIs with clopidogrel could increase the risk of cardiovascular events.

Introduction

Dual antiplatelet therapy (DAPT), with an oral $P2Y_{12}$ inhibitor and aspirin, is the cornerstone treatment for patients undergoing percutaneous coronary intervention (PCI) [1. Antiplatelet therapy reduces recurrent major adverse cardiovascular events by inhibiting platelet activation and aggregation [2]. Compared to mono-antiplatelet therapy, DAPT imparts more intense platelet inhibition and subsequent incremental reduction in thrombotic events after PCI [2]. However, concomitantly, they increase the risk of gastrointestinal (GI) bleeding [3]. Therefore, ACC/AHA guidelines recommend proton pump inhibitors (PPIs) for gastric protection in patients receiving DAPT, if the patients are at a high risk of GI bleeding (such as a history of GI hemorrhage/ulcer, chronic use of corticosteroids/non-steroidal anti-inflammatory drugs, anticoagulant therapy, or two or more of the following: age ≥ 65 years, dyspepsia, gastro-esophageal reflux disease (GERD), *Helicobacter pylori* infection, or chronic alcohol consumption) [4].

Among $P2Y_{12}$ inhibitors, clopidogrel is widely known for drug-drug interactions with some PPIs. Pharmacokinetically, clopidogrel is metabolized, primarily by CYP2C19, into an active metabolite, and omeprazole and esomeprazole (inhibiting PPIs) inhibit clopidogrel's metabolization, on co-administration with clopidogrel [5–8]. Inhibiting clopidogrel's metabolization reduces the active metabolite concentration and increases cardiovascular events after PCI [9]. Therefore, in 2009, the United States Food and Drug Administration (FDA) warned against the concomitant use of clopidogrel and inhibiting PPIs (particularly omeprazole) [10]. They recommended other drugs, such as alternate PPIs or H2 receptor antagonists (H2RAs) as antisecretory agents for patients prescribed clopidogrel [10]. Prior studies examined trends in clopidogrel and PPI use after the FDA warning and reported significant changes in prescriptions [11–13], which changed the landscape for antisecretory agents. In 2019, some ranitidine products containing *N*-nitroso-dimethylamine as an impurity, which can increase the risk of cancer, were withdrawn from the market [14]. Moreover, in 2019, a new potassium competitive acid blocker (P-CAB), tegoprazan, was approved by the Ministry of Food and Drug Safety and was subsequently used as an antisecretory agent. In this study, we aimed to evaluate trends in the use of antisecretory agents among patients administered clopidogrel-based DAPT and investigate the status of using clopidogrel and inhibiting PPIs concomitantly.

Methods

Study Data

We used the Health Insurance Review & Assessment Service National Inpatient Sample data from 2009 to 2020, which randomly selected 10–13% of the inpatients in Korea and extracted their medical records.

The International Classification of Diseases, Tenth Revision codes, were used to identify diagnostic information for patient encounters. The HIRA datasets include medical practices and prescription data in the Korean National Health Insurance (NHI) Service. There are the following three types of health insurance plans in Korea: NHI, Medical Aid (MedAid), and Patriots & Veterans Insurance (PVI). Approximately 97% of South Korea's population is enrolled in the NHI, while 3% are in the MedAid plan, a type of health insurance that offers low-income families access to affordable medical treatment, and 0.5% of the population are in the PVI plan. Drug codes (Supplementary Table 1) were used to extract information regarding antisecretory agents and antiplatelet therapy.

Study Population

First, we selected patients who underwent PCI between January and November each year using procedure codes (Supplementary Table 1). If the patient received PCI more than once during the period, only the first PCI episode was considered. Two weeks after PCI is defined as the window period [15], and the first outpatient records from the same medical institution where PCI was performed within the window period were investigated. If this outpatient prescription included both clopidogrel and aspirin, it was classified as clopidogrel-based DAPT. If there were two or more types of $P2Y_{12}$ inhibitors, the drug with the longest duration of administration was selected. The DAPT period was defined as the duration of taking clopidogrel and aspirin concurrently. Patients who benefited from the PVI were excluded. Only outpatient prescriptions were primarily included in our study, and long-term hospitalized patients were excluded because they mainly received inpatient services.

Use of Antisecretory Agents

We defined the concomitant use of antisecretory agents and clopidogrel when an antisecretory agent was newly prescribed or resumed during the DAPT period. The following three types of antisecretory agents were investigated: PPIs (dexlansoprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, and *S*-pantoprazole), H2RAs (cimetidine, famotidine, lafutidine, nizatidine, ranitidine, and roxatidine), and P-CABs (revaprazan and tegoprazan).

Statistical Analyses

Univariate statistics were used to describe the general features of patients and medical institutions. For categorical variables, the data were illustrated as counts and percentages. P-value was calculated using chi-squared tests for categorical variables. Demographic characteristics included individual factors (age and sex), social factors (insurance coverage), and health factors (hypertension, chronic heart failure, diabetes, dyslipidemia, arrhythmia, liver disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, malignancy, rheumatic disease, peptic ulcer, GERD, dyspepsia, or GI bleeding). We grouped the study population by age: ≤54, 55–59, 60–64, 65–69, 70–74, and ≥ 75 years.

Antisecretory agent use was investigated in patients undergoing clopidogrel-based DAPT. When an antisecretory agent was prescribed at least for one day during the window period, it was regarded as concurrent use. Among antisecretory agents, we focused on all PPIs, particularly inhibiting PPIs. We also determined antisecretory agent use in patients receiving other DAPT therapies, including ticagrelor, prasugrel, and ticlopidine. We aimed to compare and contrast the use of antisecretory agents in two patient groups. To ascertain the annual trend of drug utilization, we used the Cochran–Armitage trend test.

Data were analyzed using R Statistical Software (version 3.5.1; R Foundation for Statistical computing, Vienna, Austria) with statistical significance set at a *p*-level of < 0.05.

Results

Characteristics of Study Population

The number of patients undergoing PCI during the study period was 74,426. Among them, 35,277 patients had outpatient follow-up visits within the window period; among these, we identified 23,134 patients receiving clopidogrel and aspirin (Fig. 1). The age group accounting for the majority of the study population was the group aged ≤ 54 years (20.8%), followed by the group aged ≥ 75 years (19.5%). There were more male patients than female patients (69.4% vs 30.6%) in the study (Table 1).

Table 1
Demographic characteristics and antisecretory drug utilization

		Clopidogrel + ASA		Antisecretory drugs			PPIs			H2RAs			P-CABs		
		n	(%)	n	(%)	*p*-value	n	(%)	*p*-value	n	(%)	*p*-value	n	(%)	*p*-value
Overall		23,134		12,306	(53.2)		6,828	(55.5)		7,114	(57.8)		166	(1.3)	
Age	≤ 54	4,820	(20.8)	2,037	(42.3)	< 0.001	1,029	(50.5)	< 0.001	1,171	(57.5)	< 0.001	25	(1.3)	0.104
	55–59	3,092	(13.4)	1,472	(47.6)		788	(53.5)		821	(55.8)		19	(1.3)	
	60–64	3,475	(15.0)	1,801	(51.3)		1,028	(57.1)		1,008	(56.0)		18	(1.0)	
	65–69	3,635	(15.7)	2,079	(57.2)		1,124	(54.1)		1,251	(60.2)		31	(1.5)	
	70–74	3,611	(15.6)	2,086	(57.8)		1,130	(54.2)		1,299	(62.3)		21	(1.0)	
	≥ 75	4,501	(19.5)	2,831	(62.9)		1,729	(61.1)		1,564	(55.2)		52	(1.8)	
Sex	Male	16,049	(69.4)	8,015	(49.9)	< 0.001	4,396	(54.8)	0.052	4,552	(56.8)	0.002	95	(1.2)	0.031
	Female	7.085	(30.6)	4,291	(60.6)		2,432	(56.7)		2,562	(59.7)		71	(1.7)	
Insurance	NHI	21,764	(94.1)	11,429	(52.5)	< 0.001	6,313	(55.2)	0.045	6,586	(57.6)	0.136	151	(1.3)	0.336
	MedAid	1,370	(5.9)	877	(64.0)		515	(58.7)		528	(60.2)		15	(1.7)	
Hypertension	No	7,223	(31.2)	3,716	(51.4)	< 0.001	2,176	(58.6)	< 0.001	2,000	(53.8)	< 0.001	60	(1.6)	0093
	Yes	15,911	(68.8)	8,590	(54.0)		4,652	(54.2)		5,114	(59.5)		106	(1.2)	
CHF	No	19,355	(83.7)	10,074	(52.0)	< 0.001	5,422	(53.8)	< 0.001	5,969	(59.3)	< 0.001	126	(1.3)	0.045
	Yes	3,779	(16.3)	2,232	(59.1)		1,406	(63.0)		1,145	(51.3)		40	(1.8)	
Diabetes Mellitus	No	12,397	(53.6)	6,554	(52.9)	0.284	3,653	(55.7)	0.548	3,714	(56.7)	0.006	107	(1.6)	0.004
	Yes	10,737	(46.4)	5,752	(53.6)		3,175	(55.2)		3,400	(59.1)		59	(1.0)	
Dyslipidemia	No	6,673	(28.4)	3,297	(49.4)	< 0.001	1,768	(53.6)	0.004	1,955	(59.3)	0.043	55	(1.7)	0.063
	Yes	16.461	(71.1)	9,009	(54.7)		5,060	(56.2)		5,159	(57.3)		111	(1.2)	
Arrhythmia	No	21,565	(93.2)	11,390	(52.8)	< 0.001	6,189	(55.2)	0.064	6,584	(57.8)	0.974	157	(1.4)	0.318
	Yes	1,569	(6.8)	916	(58.4)		639	(58.3)		530	(57.9)		9	(1.0)	
Liver disease	No	21,281	(92.0)	11,210	(52.7)	< 0.001	5,888	(54.4)	0.049	6,512	(58.1)	0.043	154	(1.4)	0.445
	Yes	1,853	(8.0)	1,096	(59.1)		591	(56.9)		602	(54.9)		12	(1.1)	
Peripheral vascular disease	No	22,402	(95.3)	11,699	(53.1)	0.105	6,482	(55.4)	0.441	6,755	(57.7)	0.495	157	(1.3)	0.770
	Yes	1,092	(4.7)	607	(55.6)		346	(57.0)		359	(59.1)		9	(1.5)	
Cerebrovascular disease	No	21,869	(94.5)	11,515	(52.7)	< 0.001	6,364	(55.3)	0.063	6,659	(57.8)	0.866	155	(1.3)	0.916
	Yes	1,265	(5.5)	791	(62.5)		464	(58.7)		455	(57.5)		11	(1.4)	
Chronic pulmonary disease	No	21,637	(93.5)	11,384	(52.6)	< 0.001	6,248	(54.9)	< 0.001	6624	(58.2)	0.003	155	(1.4)	0.670
	Yes	1,497	(6.5)	922	(61.6)		580	(62.9)		490	(53.1)		11	(120)	
Malignancy	No	22,705	(98.1)	12,049	(53.1)	0.005	6,698	(55.6)	0.110	6,951	(57.7)	0.086	163	(1.4)	1.000
	Yes	429	(1.9)	257	(59.9)		130	(50.6)		162	(63.0)		3	(1.2)	
Rheumatic disease	No	23,037	(99.6)	12,244	(53.1)	0.034	6,797	(55.5)	0.384	7,075	(57.8)	0.416	165	(1.3)	0.570

CHF, congestive heart failure, PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; ASA, aspirin; PPIs, proton pump inhibitor; H2RAs, H2 receptor potassium competitive acid blockers; inhibiting PPIs, omeprazole, esomeprazole; non-inhibiting PPIs, dexlansoprazole, ilaprazole, lansoprazole, pantoprazole rabeprazole; †, Fisher's exact test; The sum of the percentages may exceed 100%

		Clopidogrel + ASA		Antisecretory drugs			PPIs			H2RAs			P-CABs		
	Yes	97	(0.4)	62	(63.9)		31	(50.0)		39	(62.9)		1	(1.6)	
PUD	No	22,090	(95.5)	11,566	(52.4)	< 0.001	6,512	(56.3)	< 0.001	6,607	(57.1)	< 0.001	157	(1.4)	0.747
	Yes	1,044	(4.5)	740	(70.9)		316	(42.7)		507	(68.5)		9	(1.2)	
GERD	No	18,049	(78.0)	8,027	(44.5)	< 0.001	3,194	(39.8)	< 0.001	5,728	(71.4)	< 0.001	105	(1.3)	0.591
	Yes	5,085	(22.0)	4,279	(84.1)		3,634	(84.9)		1,386	(32.4)		61	(1.4)	
Dyspepsia	No	22,777	(98.5)	12,025	(52.8)	< 0.001	6,650	(55.3)	0.007	6,966	(57.9)	0.078	161	(1.3)	0.433
	Yes	357	(1.5)	281	(78.7)		178	(63.3)		148	(52.7)		5	(1.8)	
Gastrointestinal bleeding	No	22,977	(99.3)	12,207	(53.1)	0.013	6,754	(54.5)	< 0.001	7,073	(57.9)	0..001	163	(1.3)	0.149
	Yes	157	(0.7)	99	(63.0)		74	(73.0)		41	(41.4)		3	(3.0)	
Year	2009	1,666	(7.2)	578	(34.7)	< 0.001	137	(23.7)	< 0.001	477	(82.5)	< 0.001	11	(1.9)	< 0.001
	2010	1,838	(7.9)	626	(34.1)		174	(27.8)		501	(80.0)		6	(1.0)	
	2011	1,868	(8.1)	790	(42.3)		219	(27.7)		649	(82.2)		6	(0.8)	
	2012	2,454	(10.6)	1,113	(45.4)		381	(34.2)		860	(77.3)		4	(0.4)	
	2013	2,216	(9.6)	1,124	(50.7)		464	(41.3)		790	(70.3)		2	(0.2)	
	2014	2,186	(9.5)	1,138	(52.1)		600	(52.7)		691	(60.7)		0	(0)	
	2015	2,012	(8.7)	1,142	(56.8)		636	(55.7)		691	(60.5)		2	(0.2)	
	2016	2,095	(9.1)	1,276	(60.9)		805	(63.1)		686	(53.8)		2	(0.2)	
	2017	1,636	(7.1)	1,029	(62.9)		705	(68.5)		497	(48.3)		0	(0)	
	2018	1,596	(6.9)	1,064	(66.7)		788	(74.1)		472	(44.4)		0	(0)	
	2019	1,813	(7.8)	1,215	(67.0)		926	(76.2)		494	(40.7)		38	(3.1)	
	2020	1,754	(7.6)	1,211	(69.0)		993	(82.0)		306	(25.3)		95	(7.8)	

CHF, congestive heart failure, PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; ASA, aspirin; PPIs, proton pump inhibitor; H2RAs, H2 receptor potassium competitive acid blockers; inhibiting PPIs, omeprazole, esomeprazole; non-inhibiting PPIs, dexlansoprazole, ilaprazole, lansoprazole, pantoprazole rabeprazole; †, Fisher's exact test; The sum of the percentages may exceed 100%

Figure 1

Table 1

Use of Antisecretory Agents

Among the 23,134 patients, 53.2% (n = 12,306) were prescribed one or more antisecretory drugs. H2RAs were the most preferred antisecretory agents during the study period, which accounted for 57.8% (n = 7,114) of the antisecretory drugs used. PPI accounted for 55.5% (n = 6,828), and P-CAB accounted for 1.3% (n = 166). Among the clopidogrel-based DAPT users, 2,025 patients used inhibiting PPI (8.8%), accounting for 16.5% of the antisecretory users (Table 1) and 29.7% of the PPI users.

Temporal Trend of Antisecretory Agents

Table 1 and Fig. 2 show the temporal trend of antisecretory agent use. From 2009 to 2020, the H2RA users decreased steadily. H2RA users accounted for 82.5% (n = 477) of the antisecretory drugs users in 2009, but accounted for 25.3% (n = 306) in 2020 (Cochran–Armitage trend test; $p < 0.001$). In contrast, PPI use more than tripled from 2009 to 2020 (23.7–82.0%, $p < 0.001$). Inhibiting PPI use increased 25%-points from 2009 to 2020 (4.2–30.7%, $p < 0.001$). P-CAB was rarely used before 2019, but in 2020, it accounted for 7.8% (n = 95) of the total antisecretory agent usage.

Figure 2

Discussion

In this study, we found an overall increase in antisecretory drug use in patients receiving clopidogrel-based DAPT during the study period. From 2009 to 2020, the use of antisecretory drugs nearly doubled (from 34.7–69.0%) (Table 1). This increase can be attributed to the following two phenomena. First, the number of elderly patients above 65 years of age administered clopidogrel-based DAPT increased. Older patients accounted for 44.8% (n = 747) of the patients

undergoing clopidogrel-based DAPT in 2009, which increased to 54.2% (n = 950) in 2020 (Supplementary Table 2). Thus, an almost 10% increase was observed, and the increasing trend was statistically significant ($p < 0.001$). Second, the number of patients with GERD also increased from 4.6% (n = 77) in 2009 to 38.3% (n = 671) in 2020 ($p < 0.001$). A previous study found a similar increasing trend in patients with GERD who received PPIs from 2012 to 2016 [16].

We further observed a steady increase in PPI prescriptions. Despite the FDA recommendation in 2009 and tegoprazan introduction in 2019, the rate of PPI uses increased to 82.0% (n = 993) of the antisecretory agent usage in 2020. This accounted for 56.6% of the clopidogrel-based DAPT users. PPI has been demonstrated to be superior to H2RA in the treatment of GERD and erosive/non-erosive reflux disease [17]. Ranitidine, a commonly used H2RA, was also withdrawn in 2019 due to NMDA [14]. Therefore, in 2019, H2RA accounted for 40.7% (n = 494) of the antisecretory drugs, which declined to 25.3% in 2020. As the usage of H2RA decreased, it was replaced with PPI and P-CAB.

The FDA warnings substantially altered the antisecretory prescriptions in patients using clopidogrel [11, 12, 18]. Prescriptions of inhibiting PPI in patients using clopidogrel decreased substantially after 2009 [11, 12]. One study found a reduction of 50% in patients using esomeprazole with clopidogrel (42.3–26.8% of PPI users) after the FDA safety communication [12]. Another study found that the prevalence of using inhibiting PPIs with clopidogrel declined to 0.8% at the end of 2016 [11]. In contrast, our results were different from those of previous studies.

The inhibiting PPI prescriptions increased proportionally with an increase in PPI prescriptions. Inhibiting PPIs should be avoided in patients administered clopidogrel since the concurrent use of both drugs can lead to harmful clinical outcomes [19]. Omeprazole and esomeprazole increase the risk of major adverse cardiovascular events in patients administered clopidogrel (odds ratio (OR): 1.40 vs 1.59; confidence interval (CI): 1.15–1.70 vs 1.29–1.95; respectively) [19]. However, inhibiting PPIs accounted for one-third of the PPI use in clopidogrel users. In addition, the proportion of inhibiting PPI use in patients administered clopidogrel-based DAPT. Compared to the proportion of patients administered PPIs with clopidogrel in 2009, those in 2020 increased by approximately seven-fold (4.2% vs 30.7%). It is presumed that healthcare providers did not recognize potential pharmacodynamic/pharmacokinetic drug interactions between clopidogrel and the inhibiting PPIs. According to our analysis, inhibiting PPIs accounted for 17.1% of PPI in other DAPT users, 19.1% in prasugrel-based DAPT users, and 20.0% in ticagrelor-based DAPT users (Supplementary Table 3). This indicates that clinicians select PPIs without recognizing their differences in terms of drug interactions with $P2Y_{12}$ inhibitors.

The systemic limitation is also a problem., A drug utilization review (DUR) system in South Korea monitors the prescription of drugs in real-time. In 2010, this system was nationally adopted to reduce adverse drug events [20]. This system can detect drug-drug interactions and contraindications. However, co-prescription of clopidogrel and inhibiting PPIs is not registered as a contraindicated drug pair in the current DUR system. Therefore, clinicians are not notified when they simultaneously prescribe these two drugs.

In 2019, tegoprazan was approved by the Ministry of Food and Drug Safety to be used as an antisecretory agent. Our study showed that, in 2020, 5.4% of the clopidogrel-based DAPT users and 5.6% of all types of DAPT users used P-CAB; P-CAB's applicability in therapy is not yet established. Clopidogrel is an important medication for patients who underwent PCI; hence, drugs influencing clopidogrel's activity should be avoided.

There are a few limitations in our study that warrant discussion. First, the dataset's initial purpose was not for research; instead, it was to handle insurance benefits. Second, in the prevalence measurement of clopidogrel use with PPI, we were unable to verify the patient's contraindications, drug allergies, and the patient's exact clinical laboratory data.

Despite these limitations, this study is meaningful. Few studies have examined the trend in clopidogrel and antisecretory agent use. However, we examined that many prescriptions did not consider the interaction of clopidogrel and inhibiting PPIs.

Thus, clinician negligence and loopholes in the DUR system contribute to the continued prescribing of clopidogrel and inhibiting PPIs.

Conclusions

Our study demonstrates that the use of inhibiting PPIs as well as antisecretory agents with clopidogrel increased steadily in patients undergoing PCI in Korea. This is a big concern since the increase in the use of inhibiting PPIs could increase the risk of cardiovascular events if co-administered with clopidogrel.

Declarations

Acknowledgments

We used the Health Insurance Review & Assessment Service (HIRA) National Inpatient Sample from 2009 to 2020 (S20220802003) for this study. But the results have no concern with the Ministry of Health and Welfare or HIRA.

Ethics Approval

This study was approved by the Institutional Review Board of the Pusan National University (PNU IRB/2022_115_HR).

Consent to participate

Not applicable

Consent to publish

Not applicable

Competing interests

The authors declare that there were no potential conflicts of interest in connection with the research, authorship, and/or publication of this article.

Authors' contributions

SP and NKJ conceived and designed the study; YL and HC performed the analysis; YL first drafted the manuscript; All authors participated in drafting the article and approved the final version to be submitted for publication.

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Data availability

The authors used the HIRA-NIS data for this study and do not have

permission to share these data. Raw data can be accessed with permission from Health Insurance Review and Assessment Service in Korea (http://opendata.hira.or.kr).

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Figures

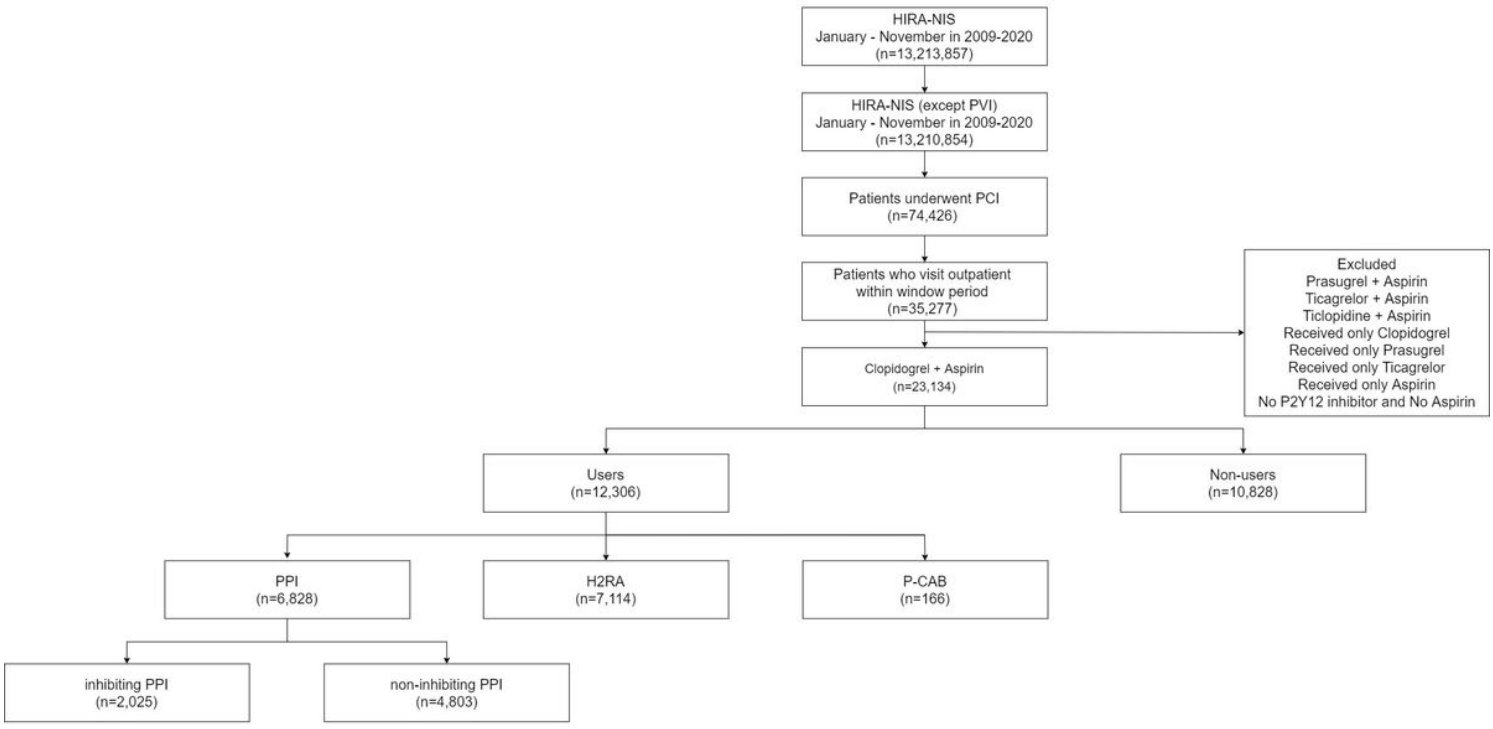

Figure 1

Case extraction diagram

HIRA, Health Insurance Review & Assessment Service; NIS, National Inpatient Sample; PVI, Patriots & Veterans Insurance; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist; P-CAB, potassium competitive acid blocker; inhibiting PPIs, omeprazole and esomeprazole; non-inhibiting PPIs: dexlansoprazole, ilaprazole, lansoprazole, pantoprazole, S-pantoprazole, and rabeprazole

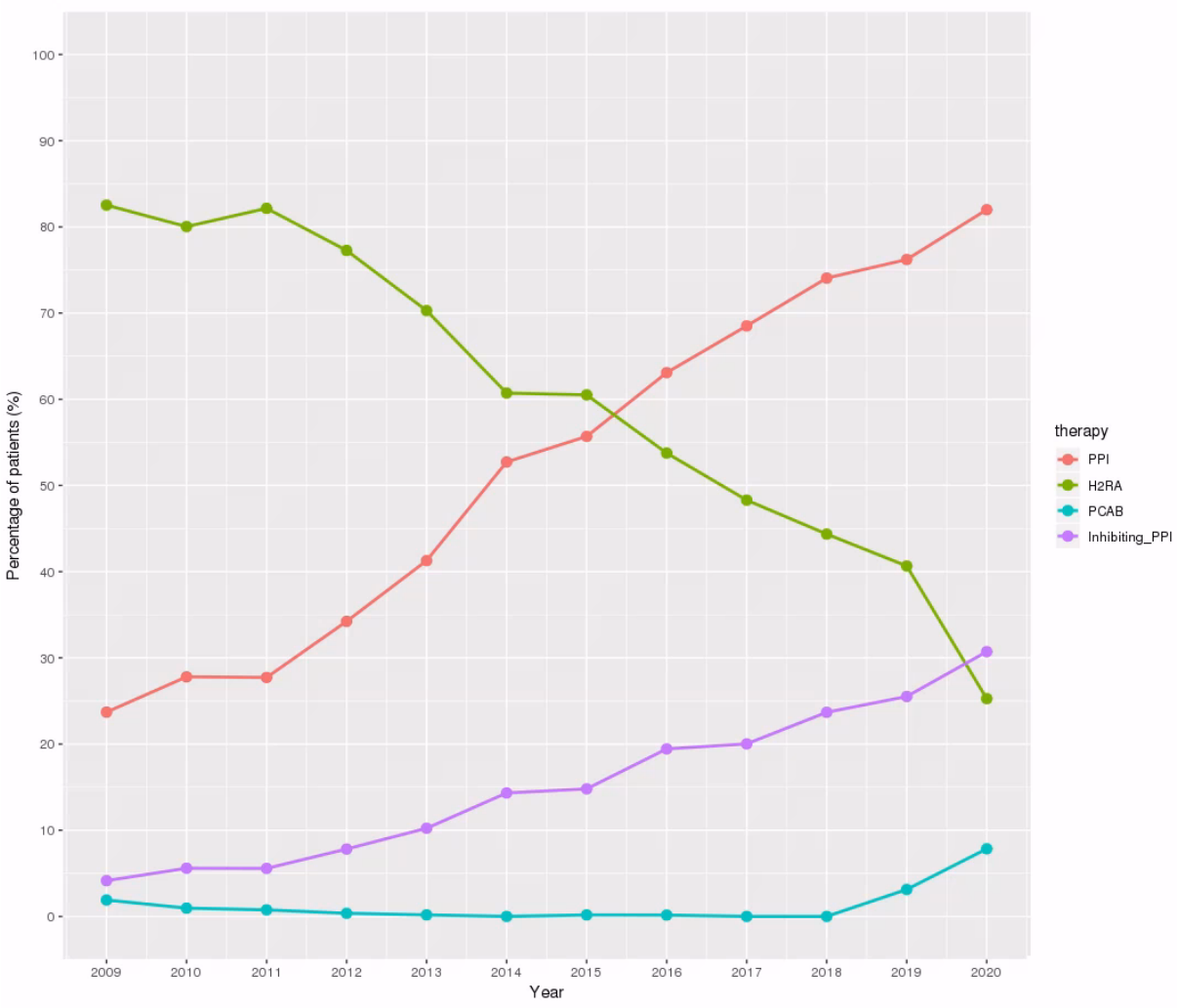

Figure 2

Antisecretory drug use from 2009 to 2020

PPIs, proton pump inhibitors; H2RAs, H2 receptor antagonist; P-CABs, potassium competitive acid blockers; inhibiting PPIs, omeprazole and esomeprazole; The sum of percentages may exceed 100 %

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