Clinical Study Report Synopsis

Drug Substance	PPI and H_2RAs
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Association between acid-suppressing drug use and risk of seizure

Study dates: Retrospective, observational, cohort study covering the period January 2005 – December 2011

Phase of development: Therapeutic use

Principal Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

Study centre(s)

UK

Objectives

- To estimate the incidence of seizure in the general population, overall and stratified by epilepsy status.
- To estimate the relative risk of seizure associated with use of proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H_2RAs), overall and stratified by epilepsy status.

Study design

A retrospective, observational, cohort study with nested case–control analysis, performed using data from The Health Improvement Network (THIN) primary care database in the UK.

Identification of participants

Individuals aged 20–84 years between 1 January 2005 and 31 December 2011, who had been enrolled with their primary care physician (PCP) for at least 2 years and had a computerized prescription history of at least 1 year were identified from THIN. Individuals with a history of cancer, drug or alcohol abuse, or alcohol-related disease were excluded.

Follow-up

All 2 289 692 individuals in the study cohort were followed up from their start date until they reached one of the following endpoints: seizure diagnosis; their 85th birthday; occurrence of a study exclusion criterion (cancer, drug or alcohol abuse, or alcohol-related disease); death; or end of study period (31 December 2011).

Seizure case ascertainment

Potential seizure cases were identified from THIN records using an automated computer search for specific Read codes and were ascertained by manual review of electronic medical records. A total of 8605 seizure cases were identified. Of these, 5510 (64%) occurred in patients with a pre-existing diagnosis of epilepsy and 3095 (36%) occurred in those with no previous epilepsy diagnosis.

Categorization according to exposure and non-exposure to PPIs and H_2RAs

A nested, case–control analysis was conducted to estimate the risk of seizure associated with acid-suppressing medication use. For the analysis, 40 000 controls from the study cohort were calendar-year frequency matched to the 8605 seizure cases. Use of acid-suppressing medication was categorized as follows: 1) current use, when the supply of the most recent prescription lasted until the index date; 2) recent use, when the supply of the most recent prescription ended 1–90 days before the index date; 2) past use, when the supply of the most recent prescription ended 91–365 days before the index date; and 4) non-use, when there was no recorded use of the relevant medication in the 365 days before the index date. PPIs and H_2RAs were considered separately.

Current use was analysed further according to the duration of treatment (≤ 3 months, 4–12 months or > 12 months) and treatment dose (low, medium or high). The following were defined as medium daily doses: esomeprazole 40 mg; omeprazole 20 mg; lansoprazole 30 mg; pantoprazole 40 mg; rabeprazole 20 mg; cimetidine 800 mg; famotidine 40 mg; nizatidine 300 mg; and ranitidine 300 mg. Doses below or above these values were defined as low and high daily doses, respectively.

Data collection and analysis

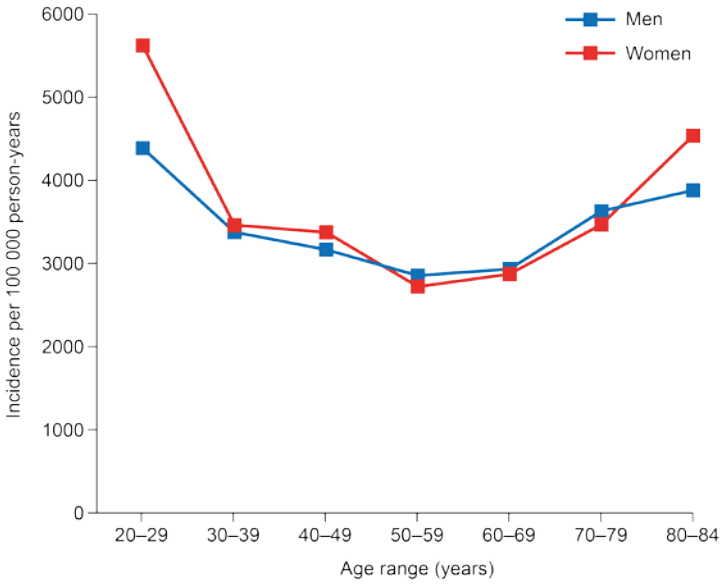
The incidence of seizure was calculated in the entire study cohort, and also separately for men and women, and for those with epilepsy and without. Two different unconditional logistic regression models were used to assess the effect of exposure to acid-suppressing drugs on seizure risk. Both models were adjusted for PPI and/or H_2RA use, sex, age, time to event, calendar year, healthcare utilization (PCP visits, referrals and hospitalizations), alcohol and/or tobacco use, socioeconomic status, body mass index, polypharmacy, history of previous seizure, cerebrovascular accident, traumatic brain injury, multiple sclerosis, metabolic alterations and drug allergy/poisoning. In addition to the aforementioned factors, model 1 was adjusted for peripheral artery disease, history of dementia/psychosis, mental retardation, osteoarthritis, diabetes mellitus, depression, neuralgia, migraine, peptic ulcer disease, dyspepsia, coeliac disease, and use of antiepileptic drugs, antidepressants, hypnotics, anxiolytics, antihypertensives, insulin, glucagon-like peptide-1, nitrates, paracetamol and/or acetylsalicylic acid. Central nervous system infections were included as an additional variable in model 2 only. Demographic factors, comorbidities and medication use were also assessed as potential risk factors for seizure. Nominal *p* values were reported for the various subgroups using the two models with no adjustments for multiplicity.

Summary of results

Incidence of seizure

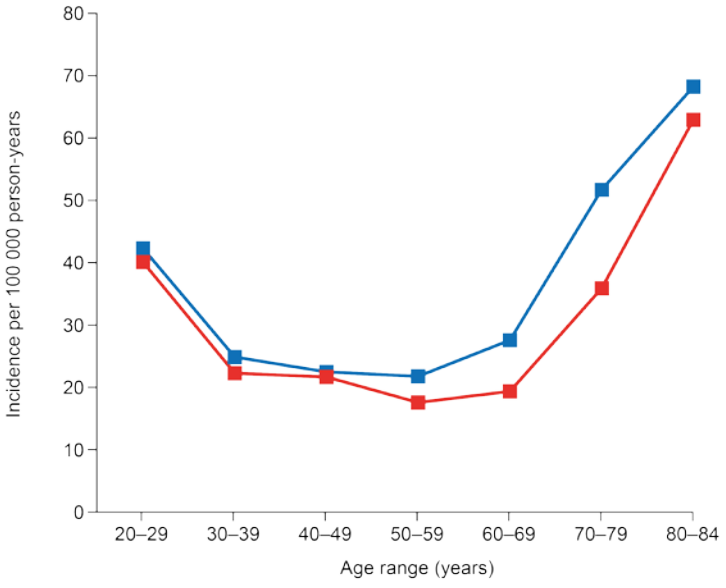
Crude incidences of seizure in men and women are shown in Figure 1 according to epilepsy status. The overall incidence of seizure was 76.10 per 100 000 person-years and was higher in men (79.14 per 100 000 person-years) than in women (73.45 per 100 000 person-years). The incidence of seizure was substantially higher in the epilepsy subcohort (3445.17 per 100 000 person-years) than in the non-epilepsy subcohort (27.76 per 100 000 person-years).

a)



Men	4387.4	3377.5	3166.1	2852.2	2933.5	3629.5	3879.8
Women	5622.5	3462.1	3375.2	2721.0	2872.4	3468.1	4537.7

b)



Men	42.3	24.9	22.5	21.8	27.6	51.7	68.2
Women	40.1	22.3	21.7	17.6	19.4	35.9	62.9

Figure 1. Incidence of seizure per 100 000 person-years in men and women (a) with epilepsy and (b) without.

Risk of seizure associated with exposure to acid-suppressing drugs
Odds ratios (with 95% confidence intervals [CIs]) for the risk of seizure associated with PPI and H_2RA use are shown in Table 1. In both models, current, recent or past exposure to PPIs or H_2RAs was not associated with increased odds of having a seizure. In subanalyses, high-dose PPI use for longer than 12 months was not associated with an increased risk of seizure when using model 2; however, a trend towards an increased risk was observed when using model 1. Long-term, medium- or low-dose PPI treatment was not associated with an increased risk of seizure, neither when using model 2 nor when using model 1.

Table 2 summarizes odds ratios (with 95% CIs) for the risk of seizure associated with PPIs and H_2RAs for the subcohorts with and without epilepsy. In both models, current, recent or past exposure to PPIs was not associated with increased odds of having a seizure in the epilepsy subcohort or the non-epilepsy subcohort. In subanalyses, long-term, high-dose PPI use for longer than 12 months was not associated with an increased risk of seizure in the epilepsy subcohort. In the non-epilepsy subcohort, high-dose PPI use for longer than 12 months was not associated with an increased risk of seizure when using model 2, but an increased risk of seizure was observed with model 1. For H_2RAs, current, recent or past exposure was not associated with increased odds of having a seizure in the non-epilepsy cohort. In the epilepsy cohort, none of the controls and fewer than 1% of the cases were current or past H_2RA users when they had a seizure and odds ratios could thus not be calculated.

Table 1. Odds ratios for seizure associated with PPI or H_2RA use.

	Cases (n = 8605)n (%)	Controls (n = 40 000)n (%)	Model 1[a] Adjusted OR (95% CI)	*p* value	Model 2[b] Adjusted OR (95% CI)	*p* value
PPIs,[c]						
Current use	383 (4.5)	1001 (2.5)	1.11 (0.91–1.36)	0.30	1.05 (0.87–1.27)	0.64
≤ 3 months	108 (1.3)	320 (0.8)	1.26 (0.90–1.75)	0.17	1.17 (0.85–1.62)	0.33
4–12 months	117 (1.4)	270 (0.7)	0.94 (0.66–1.34)	0.73	0.97 (0.69–1.35)	0.85
> 12 months	158 (1.8)	411 (1.0)	1.14 (0.84–1.53)	0.40	1.02 (0.76–1.35)	0.91
Low dose						
≤ 3 months	20 (0.2)	54 (0.1)	1.67 (0.82–3.43)	0.16	1.61 (0.80–3.21)	0.18
4–12 months	21 (0.2)	61 (0.2)	1.37 (0.67–2.78)	0.39	1.27 (0.64–2.51)	0.50
> 12 months	37 (0.4)	134 (0.3)	0.86 (0.47–1.57)	0.62	0.72 (0.41–1.27)	0.26
Medium dose						
≤ 3 months	74 (0.9)	238 (0.6)	1.34 (0.92–1.95)	0.13	1.24 (0.85–1.79)	0.27
4–12 months	80 (0.9)	183 (0.5)	0.85 (0.56–1.31)	0.46	0.89 (0.60–1.33)	0.57
> 12 months	101 (1.2)	229 (0.6)	1.21 (0.83–1.75)	0.32	1.20 (0.84–1.71)	0.31
High dose						
≤ 3 months	12 (0.1)	28 (0.1)	0.95 (0.34–2.63)	0.92	0.83 (0.30–2.29)	0.72
4–12 months	15 (0.2)	24 (0.1)	1.09 (0.44–2.72)	0.85	1.35 (0.55–3.33)	0.52
> 12 months	20 (0.2)	45 (0.1)	2.00 (0.99–4.00)	0.05	1.58 (0.79–3.16)	0.19
Multiple use	3 (0.03)	5 (0.01)	0.62 (0.02–15.59)	0.77	0.47 (0.01–15.73)	0.68
Recent use	221 (2.6)	686 (1.7)	0.92 (0.71–1.18)	0.49	0.93 (0.73–1.19)	0.56
Past use	260 (3.0)	979 (2.4)	1.16 (0.94–1.44)	0.16	1.10 (0.90–1.35)	0.34
H_2RAs[c],						
Current use	42 (0.5)	80 (0.2)	1.32 (0.69–2.52)	0.40	1.16 (0.62–2.18)	0.64
≤ 3 months	30 (0.3)	38 (0.1)	2.04 (0.92–4.54)	0.08	1.71 (0.77–3.78)	0.19
4–12 months	8 (0.1)	22 (0.1)	1.37 (0.37–5.07)	0.64	1.10 (0.31–3.90)	0.88
> 12 months	4 (0.05)	20 (0.1)	0.23 (0.04–1.50)	0.12	0.30 (0.05–1.80)	0.19
Low dose	3 (0.0)	11 (0.0)	1.01 (0.18–5.53)	1.00	1.02 (0.18–5.72)	0.98
Medium dose	30 (0.3)	60 (0.1)	1.22 (0.56–2.65)	0.62	1.07 (0.51–2.28)	0.85
High dose	3 (0.03)	3 (0.01)	3.20 (0.26–39.04)	0.36	2.39 (0.21–27.59)	0.49

≤ 3 months	30 (0.3)	38 (0.1)	–[d]		–[d]	
4–12 months	8 (0.1)	22 (0.1)	–[d]		–[d]	
> 12 months	4 (0.05)	20 (0.1)	0.72 (0.01–51.77)	0.88	0.68 (0.02–30.45)	0.84
Recent use	16 (0.2)	70 (0.2)	0.67 (0.28–1.61)	0.37	0.67 (0.28–1.58)	0.36
Past use	40 (0.5)	132 (0.3)	0.84 (0.48–1.48)	0.55	0.85 (0.49–1.47)	0.57

[a]Logistic regression model adjusted for: PPI and/or H_2RA use; sex; age; time to event; calendar year; healthcare utilization (PCP visits, referrals and hospitalizations); alcohol and/or tobacco use; socioeconomic status; BMI; polypharmacy; peripheral artery disease; history of previous seizure, dementia/psychosis, mental retardation, osteoarthritis, diabetes mellitus, depression, neuralgia, migraine, peptic ulcer disease, dyspepsia, coeliac disease, CVA, multiple sclerosis, TBI, metabolic alterations and/or drug allergy/poisoning; use of antiepileptic drugs, antidepressants, hypnotics, anxiolytics, antihypertensives, insulin, glucagon-like peptide-1, nitrates, paracetamol and/or acetylsalicylic acid.
[b]Logistic regression model adjusted for: PPI and/or H_2RA use; sex; age; time to event; calendar year; healthcare utilization (PCP visits, referrals and hospitalizations); alcohol and/or tobacco use; socioeconomic status; BMI; polypharmacy; history of previous seizure, CVA, multiple sclerosis, TBI, central nervous system infections, metabolic alterations and/or drug allergy/poisoning.
[c]Relative to non-use.
[d]None of the controls and only 0.01% of cases were current high-dose H_2RA users for 12 months or less.
BMI, body mass index; CI, confidence interval; CVA, cerebrovascular accident; H_2RA, histamine 2 receptor antagonist; OR, odds ratio; PCP, primary care physician; PPI, proton pump inhibitor; TBI, traumatic brain injury.

Table 2. Effect of PPI and H_2RA therapy on the risk of seizure in individuals with or without epilepsy.

	With epilepsy				Without epilepsy			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
PPIs[c]								
Current use	0.93 (0.52–1.68)	0.82	0.87 (0.49–1.53)	0.63	1.12 (0.91–1.38)	0.29	1.05 (0.87–1.28)	0.60
≤ 3 months	0.95 (0.31–2.94)	0.93	0.84 (0.28–2.48)	0.75	1.27 (0.90–1.80)	0.17	1.19 (0.85–1.66)	0.31
4–12 months	1.65 (0.38–7.09)	0.50	1.85 (0.44–7.79)	0.40	0.86 (0.58–1.26)	0.43	0.91 (0.64–1.29)	0.59
> 12 months	0.77 (0.37–1.61)	0.49	0.67 (0.33–1.38)	0.28	1.22 (0.90–1.65)	0.20	1.07 (0.80–1.43)	0.64
Low dose	2.20 (0.50–9.66)	0.30	1.69 (0.40–7.21)	0.48	1.11 (0.73–1.67)	0.63	1.00 (0.68–1.47)	0.99
Medium dose	0.70 (0.36–1.33)	0.28	0.72 (0.38–1.35)	0.31	1.18 (0.92–1.50)	0.19	1.15 (0.92–1.45)	0.22
High dose	1.84 (0.22–15.23)	0.57	1.29 (0.17–9.91)	0.81	1.31 (0.78–2.20)	0.30	1.21 (0.73–1.99)	0.47
≤ 3 months	–[d]		–[d]		0.86 (0.29–2.54)	0.78	0.75 (0.26–2.14)	0.59
4–12 months	–[d]		–[d]		0.85 (0.31–2.33)	0.76	1.14 (0.43–3.04)	0.79
> 12 months	1.14 (0.12–10.78)	0.91	0.63 (0.07–5.35)	0.67	2.08 (1.03–4.21)	0.04	1.59 (0.79–3.21)	0.19
Recent use	0.92 (0.48–1.77)	0.81	0.78 (0.42–1.45)	0.43	0.93 (0.71–1.21)	0.58	0.95 (0.73–1.23)	0.69
Past use	1.43 (0.67–3.08)	0.35	1.29 (0.61–2.71)	0.50	1.15 (0.92–1.44)	0.21	1.09 (0.88–1.34)	0.45
H_2RAs[c]								
Current use	–[e]		–[e]		1.12 (0.55–2.27)	0.76	1.02 (0.51–2.01)	0.96
≤ 3 months	–[e]		–[e]		1.87 (0.80–4.39)	0.15	1.54 (0.66–3.60)	0.32
4–12 months	–[e]		–[e]		1.23 (0.31–4.79)	0.77	1.02 (0.28–3.79)	0.97
> 12 months	–[e]		–[e]		0.11 (0.01–1.27)	0.08	0.19 (0.02–1.84)	0.15
Low dose	–[e]		–[e]		0.90 (0.16–5.11)	0.91	0.95 (0.16–5.61)	0.96
Medium dose	–[e]		–[e]		1.02 (0.43–2.42)	0.96	0.92 (0.41–2.10)	0.85
High dose	–[e]		–[e]		3.04 (0.23–40.44)	0.40	2.18 (0.16–29.12)	0.56
Recent use	0.83 (0.09–7.97)	0.87	0.67 (0.08–5.66)	0.71	0.71 (0.28–1.79)	0.47	0.71 (0.29–1.74)	0.46
Past use	–[f]		–[f]		0.64 (0.33–1.25)	0.20	0.67 (0.35–1.28)	0.23

[a]Logistic regression model adjusted for: PPI and/or H_2RA use; sex; age; time to event; calendar year; healthcare utilization (PCP visits, referrals and hospitalizations); alcohol and/or tobacco use; socioeconomic status; BMI; polypharmacy; peripheral artery disease; history of previous seizure, dementia/psychosis, mental retardation, osteoarthritis, diabetes mellitus, depression, neuralgia, migraine, peptic ulcer disease, dyspepsia, coeliac disease, CVA, multiple sclerosis, TBI, metabolic alterations and/or drug allergy/poisoning; use of antiepileptic drugs, antidepressants, hypnotics, anxiolytics, antihypertensives, insulin, glucagon-like peptide-1, nitrates, paracetamol and/or acetylsalicylic acid.
[b]Logistic regression model adjusted for: PPI and/or H_2RA use; sex; age; time to event; calendar year; healthcare utilization (PCP visits, referrals and hospitalizations); alcohol and/or tobacco use; socioeconomic status; BMI; polypharmacy; history of previous seizure, CVA, multiple sclerosis, TBI, central nervous system infections, metabolic alterations and/or drug allergy/poisoning.
[c]Relative to non-use.
[d]None of the controls and only 0.3% of cases were high-dose PPI users for 12 months or less.
[e]None of the controls and only 0.5% of cases were current H_2RA users.
[f]None of the controls and only 0.5% of cases were past H_2RA users.
BMI, body mass index; CI, confidence interval; CVA, cerebrovascular accident; H_2RA, histamine 2 receptor antagonist; OR, odds ratio; PCP, primary care physician; PPI, proton pump inhibitor; TBI, traumatic brain injury.

Risk factors for seizure

The effects of demographic factors, comorbidities and medication use on seizure risk are summarized in Table 3. History of epilepsy was the strongest predictor of seizure. Other comorbidities associated with increased odds of seizure included dementia/psychosis, history of seizures, cerebrovascular accident, mental retardation and multiple sclerosis. Central nervous system drugs and paracetamol were associated with an increased seizure risk, most likely because of confounding by indication. Antihypertensives, statins and oral antidiabetic agents were associated with a decreased risk of seizure.

Table 3. Effect of demographic factors and comorbidities on the risk of seizure.

		Adjusted OR (95%CI)[a]	***p* value**
Demographic factors			
Sex	Male	1 (–)	
	Female	0.80 (0.74–0.87)	< 0.01
Age, years	20–39	1 (–)	
	40–49	0.80 (0.72–0.89)	< 0.01
	50–64	0.67 (0.60–0.74)	< 0.01
	65–74	0.68 (0.59–0.77)	< 0.01
	75–84	0.91 (0.78–1.05)	0.19
BMI, kg/m^2	20–24	1 (–)	
	< 20	1.17 (1.00–1.36)	0.04
	25–29	0.84 (0.77–0.93)	< 0.01
	≥ 30	0.72 (0.65–0.81)	< 0.01
Comorbidities[b]			
History of seizures		9.03 (7.49–10.88)	< 0.01
History of epilepsy		134.55 (121.09–149.50)	< 0.01
Cerebrovascular accident[c]		4.15 (3.59–4.81)	< 0.01
Haemorrhagic stroke		6.61 (4.70–9.29)	< 0.01
Ischaemic stroke		3.88 (3.32–4.53)	< 0.01
Ischaemic heart disease		0.80 (0.67–0.94)	< 0.01
Myocardial infarction		0.81 (0.63–1.03)	0.09
Angina (stable)		0.73 (0.59–0.90)	< 0.01
Anxiety		1.22 (1.11–1.35)	< 0.01
Depression		1.35 (1.23–1.47)	< 0.01
Dementia/psychosis		9.72 (7.50–12.60)	< 0.01
Schizophrenia		1.70 (1.11–2.60)	0.02
Parkinson’s disease		2.11 (1.34–3.31)	< 0.01
Mental retardation		3.65 (2.40–5.57)	< 0.01
Migraine		1.21 (1.06–1.37)	0.01

Traumatic brain injury		1.90 (1.64–2.19)	< 0.01
Multiple sclerosis		3.26 (2.20–4.82)	< 0.01
Use of CNS drugs[d]			
Antiepileptics	Current use	2.84 (2.43–3.33)	< 0.01
	Recent use	2.68 (2.00–3.58)	< 0.01
	Past use	2.32 (1.58–3.41)	< 0.01
Anxiolytics	Current use	1.79 (1.35–2.37)	< 0.01
	Recent use	2.45 (1.89–3.18)	< 0.01
	Past use	1.74 (1.40–2.16)	< 0.01
Hypnotics	Current use	2.13 (1.67–2.72)	< 0.01
	Recent use	2.19 (1.69–2.84)	< 0.01
	Past use	1.39 (1.09–1.78)	0.01
Antidepressants	Current use	1.75 (1.54–1.98)	< 0.01
	Recent use	1.78 (1.49–2.13)	< 0.01
	Past use	1.48 (1.23–1.77)	< 0.01
Current use of non-CNS drugs[d]			
Antibiotics		1.22 (0.98–1.52)	0.08
Antihistamines		1.21 (0.94–1.54)	0.13
Antihypertensives		0.68 (0.60–0.77)	< 0.01
Statins		0.72 (0.63–0.83)	< 0.01
Oral antidiabetics		0.53 (0.43–0.67)	< 0.01
Insulin		1.07 (0.81–1.41)	0.64
Nitrates		0.77 (0.56–1.06)	0.11
Clopidogrel		0.63 (0.42–0.95)	0.03
Warfarin		0.82 (0.70–0.95)	0.01
ASA		0.84 (0.72–0.97)	0.02
NSAIDs		1.00 (0.83–1.21)	0.97
Paracetamol		1.29 (1.11–1.50)	< 0.01
Oral corticosteroids		0.68 (0.47–0.99)	0.04

[a]Logistic regression model adjusted for: PPI and/or H_2RA use; sex; age; time to event; calendar year; healthcare utilization (primary care physician visits, referrals and hospitalizations); alcohol and/or tobacco use; socioeconomic status; BMI; polypharmacy; history of previous seizure, cerebrovascular accident, multiple sclerosis, traumatic brain injury, CNS infections, metabolic alterations and/or drug allergy/poisoning.
[b]Relative to absence for each comorbidity.
[c]Overall for haemorrhagic and ischaemic stroke.
[d]Relative to non-use for each drug.
ASA, acetylsalicylic acid; BMI, body mass index; CI, confidence interval; CNS, central nervous system; H_2RA, histamine 2 receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton pump inhibitor.