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ORIGINAL RESEARCH ARTICLE

Drug Utilisation Patterns of Alternatives to Ranitidine-Containing Medicines in Patients Treated with Ranitidine: A Network Analysis of Data from Six European National Databases

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Abstract

Introduction Ranitidine, a histamine H_2-receptor antagonist (H_2RA), is indicated in the management of gastric acid-related disorders. In 2020, the European Medicines Agency (EMA) recommended suspension of all ranitidine-containing medicines in the European Union (EU) due to the presence of *N*-nitrosodimethylamine (NDMA) impurities, which were considered to be carcinogenic. The aim of this study was to investigate the impact of regulatory intervention on use patterns of ranitidine-containing medicines and their therapeutic alternatives.

Objectives The aim was to study drug utilisation patterns of ranitidine and report discernible trends in treatment discontinuation and switching to alternative medications.

Methods This retrospective, population-based cohort study was conducted using primary care records from six European countries between 2017 and 2023. To explore drug utilisation patterns, we calculated (1) incident use of ranitidine, other H_2RAs, and other alternative drugs for the treatment of gastric ulcer and/or gastric bleeding; (2) ranitidine discontinuation; and (3) switching from ranitidine to alternative drugs (H_2RAs, proton-pump inhibitors [PPIs], and other medicinal products for acid-related disorders).

Results During the study period, 385,273 new ranitidine users were observed, with most users being female and aged 18–74 years. Ranitidine was the most commonly prescribed H_2RA in the pre-referral period (September 2017–August 2019), with incidence rates between 0.8 and 9.0/1000 person years (PY). A steep decline to 0.3–3.8/1000 PY was observed in the referral period (September 2019–March 2020), eventually dropping to 0.0–0.4/1000 PY in the post-referral period (April 2020–March 2022). Switching from ranitidine to alternative drugs increased in the post-referral period, with the majority of patients switching to PPIs. Discontinuation of ranitidine use ranged from 270 to 380/1000 users in 2017 and decreased over time.

Conclusions Ranitidine was commonly used prior to referral, but it was subsequently discontinued and replaced primarily with PPIs.

Key Points

Ranitidine, previously the most prescribed histamine-2 receptor antagonist in several European countries, has been discontinued in line with the current recommendations by the European Medicines Agency.

Regulatory referral actions have significantly shaped the utilization patterns of ranitidine and its alternatives in the management of gastrointestinal conditions, with newly diagnosed cases now primarily managed using proton pump inhibitors.

This study highlights the healthcare system's ability to respond effectively to evolving drug safety considerations in patient care.

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1 Introduction

Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H_2-receptors on gastric parietal cells [1]. Ranitidine was introduced into the European market in 1981 and used for the management of acid-related disorders such as peptic ulcer disease, gastritis/duodenitis (with or without *Helicobacter pylori* [*H. pylori*]), Zollinger-Ellison syndrome, gastro-oesophageal reflux disease (GERD), post-operative ulcer, prophylaxis of stress ulceration, and chronic episodic dyspepsia. Prior to its suspension, ranitidine was available for oral and parenteral administration, and as a prescription and over-the-counter (OTC) drug for the relief of symptomatic heartburn and non-ulcer dyspepsia [2, 3].

In 2019, results of a preliminary laboratory analysis showed the presence of *N*-nitrosodimethylamine (NDMA) impurities, a potential human carcinogen, in ranitidine [4]. Further laboratory analysis showed that the NDMA levels of most ranitidine active pharmaceutical ingredients and finished products were above the acceptable intake [4]. In light of the foregoing, the European Commission initiated a referral procedure in September 2019 to assess the relevance of these findings, potential causes, and their impact on the benefit–risk balance of medicinal products containing ranitidine [5]. Based on this assessment, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the suspension of all ranitidine-containing medicines in the European Union (EU) in April 2020, as treatment alternatives for ranitidine were available [6].

Since the initiation of the referral, many ranitidine-containing medicines have been unavailable in the EU for several months because national competent authorities have either recalled them due to the presence of NDMA impurities or as a precautionary measure while the EMA review was ongoing. Patients and healthcare providers were expected to seek alternative treatment strategies as ranitidine-containing medicines were unavailable. The impact of EMA's regulatory intervention on the use patterns of ranitidine and alternative medicines to ranitidine has—to our knowledge—not yet been quantified.

The aim of this drug utilisation study is to evaluate the impact of regulatory actions taken for ranitidine-containing medicinal products following the start of the referral procedure by examining prescription patterns of ranitidine and alternative medicines over time and to investigate whether ranitidine users discontinued treatment with or without switching to alternative medicines.

2 Methods

2.1 Study Design, Setting, and Population

A retrospective population-based cohort study was conducted using electronic healthcare records from six databases in six European countries: Germany (Disease Analyser [DA], IQVIA), France (Longitudinal Patient Database [LPD], IQVIA), the United Kingdom (UK) (IQVIA Medical Research Data [IMRD]), the Netherlands (Integrated Primary Care Information [IPCI]), Belgium (LPD, IQVIA), and Spain (Information System for Research in Primary Care [SIDIAP]). All databases were primary care databases, with IQVIA Germany containing both primary care and specialist data. Detailed information on each database is provided in Supplemental Table 1 (see the electronic supplementary material). All databases were standardised and mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), which was developed by the Observational Health Data Sciences and Informatics (OHDSI) initiative to facilitate data harmonisation and standardised data analytics [7]. The study protocol has been registered with the European Union electronic Register of Post-Authorisation Studies (EU PAS Register®) (EUPAS44548). The present study spans 2 years before referral initiation (pre-referral period, September 2017–August 2019), the period between referral initiation and finalisation (in-referral period, September 2019–March 2020), and 2 years after initial CHMP recommendation for suspension of ranitidine use (post-referral period, April 2020–March 2022). Hence, data were extracted over a study period of 1 January 2017 until 1 January 2023 to cover the ranitidine pre- and post-referral periods. Thus, the study period spanned a larger time window than the referral periods. Nevertheless, analysis was done by full calendar years (2017–2022) but also by referral period using the exact time windows.

The study population comprised all patients, including both children and adults, who were registered with a general practitioner (GP) during the study period and had a continuous enrolment of 12 months in the database. Follow-up for each patient began at the start of the study period or the date the patient entered the study population and contributed active follow-up time, whichever came last. The follow-up period stopped at the end of the observation period or the end of the study period, whichever came first. Patients were excluded if they had missing age or sex.

2.2 Exposure of Interest

We used prescription and dispensing data to identify the exposures of interest, which included the following: ranitidine (Anatomical Therapeutic Chemical code (ATC) A02BA02), other histamine H_2-receptor antagonists (H_2RAs) (including cimetidine (ATC—A02BA01), famotidine (ATC—A02BA03), nizatidine (ATC—A02BA04), niperotidine (ATC—A02BA05), roxatidine (ATC—A02BA06), lafutidine (ATC—A02BA08)), PPIs (ATC—A02BC), and other medicinal products for acid-related disorders, as shown in Supplemental Table 2 (see the electronic supplementary material). We conducted an automated search using RxNorm concept codes to identify individuals within the study population who had been exposed to any of the drugs of interest. This process allowed us to create cohorts for patients exposed to each individual ingredient and their respective drug classes, including H_2RAs (excluding ranitidine), PPIs, and antacids (ATC—A02A).

2.3 Duration of Use, Dosing, and Type of Formulation of Ranitidine

Treatment episodes were calculated as the sum of the durations of the individual prescription/dispensing. A gap of more than 30 days between prescriptions, i.e. a gap of more than 30 days between the estimated end date of a drug and the start date of the same drug, signalled the end of the treatment episode, assuming continuous use. The duration of use was divided into four categories: 1–15 days, 16–30 days, 31–100 days, and more than 100 days.

The dose of ranitidine was expressed as a ratio of prescribed daily dose (PDD), the average dose prescribed per day for a drug, to defined daily dose (DDD), which is the average maintenance dose per day for a drug, according to the World Health Organization (WHO), and reported by period of use. In cases where dosing instructions were available, the PDD of a specific drug was calculated by multiplying the number of prescribed units per day by its strength. If dosing instructions were missing, the PDD was calculated by multiplying the number of pills prescribed/dispensed by its strength, and then dividing this value by the duration of the treatment episode (the sum of the duration of the individual prescriptions/dispensing of the respective drug/treatment class of interest). In cases where both dosing instructions and strength information were unavailable, the dose was estimated using the DDD as proxy [8]. The formulations of ranitidine prescription/dispensing were also reported.

2.4 Indication for Ranitidine and Use of Alternative Medicines in Patients Diagnosed with Conditions for Which Ranitidine (or Alternative Drugs) are Indicated

The indication for ranitidine use was assessed for the first prescription of a patient during each of the referral periods. The presence of predefined SNOMED codes for the gastrointestinal indications of interest was checked in a window of 180 days prior to the prescription. To describe the drug utilisation patterns of new starters of alternatives to ranitidine, we defined a cohort of patients diagnosed with conditions for which use of ranitidine was indicated (i.e. GERD, peptic ulcer disease [with or without *H. pylori*], Zollinger Ellison Syndrome, and dyspepsia/indigestion) prior to suspension.

2.5 Outcomes

The outcomes of interest were incident use, discontinuation of ranitidine treatment, and switching from ranitidine to alternative medicines. An incident user was defined as a patient with a record of the exposure of interest and no exposure within the previous 365 days. Incident drug use was investigated not only in the total study population, but also in the cohort of patients diagnosed with conditions for which ranitidine was indicated prior to ranitidine suspension. A patient was defined as discontinuing ranitidine treatment if there was a gap of more than 90 days following a ranitidine exposure during which no new ranitidine prescription or alternative treatment was initiated. Switching from ranitidine to alternative medicines (H_2RAs, PPIs, or other medicinal products for acid-related disorders) was categorised as, firstly, *early switching*, meaning a new treatment started shortly after an exposure of ranitidine or with a short overlap. The new treatment could start a maximum 15 days before the end of ranitidine exposure (i.e. overlap) and no later than 90 days after the end of the ranitidine exposure. Overlap of more than 15 days of previous use of ranitidine with use of alternative medicines was not considered as treatment switch. Secondly, *late switching* from ranitidine to alternative medicines was considered in the case where there was a gap of more than 90 but less than 365 days between the end of ranitidine exposure and the start of the alternative medicine.

2.6 Statistical Analysis

All results are presented separately by database. Age was assessed at the beginning of each calendar year and categorised into three groups (< 18 years, 18–74 years, and ≥ 75 years) to provide insight into the use of ranitidine among different age groups. Categorical variables were described by the number and percentage of patients in each group. The number of patients with missing data for key variables was reported, but no imputation was performed to deal with

missing data. Demographic profiles, indications, duration of use, and characteristics of exposure were presented for ranitidine users in the three referral periods (pre-referral, in-referral, and post-referral).

Incident drug use was expressed as the number of new users per 1000 person years (PY). For the incidence rate calculation in the cohort of patients with a diagnosed indication, the numerator was the number of incident users in the 180 days following the first diagnosis of interest, and the denominator was the person time in the 180 days following the first diagnosis of interest. Incidence of discontinuation of ranitidine and switching to alternative medications was expressed as the number of patients discontinuing and switching treatment, respectively, per 1000 ranitidine users. Incidences are presented by calendar year and by referral period.

3 Results

A total of 45,456,150 persons were observed during the study period. There were 304,968 ranitidine users in the pre-referral period, 38,691 in the in-referral period, and 14,614 in the post-referral period (Supplemental Table 1; see the electronic supplementary material). The demographic characteristics of ranitidine users by database and referral periods are presented in Supplemental Table 3. Across databases, ranitidine users were mostly females and individuals aged 18–74 years. The duration of ranitidine use was comparable across the referral periods; however, there were some database-specific differences. In DA Germany, a high proportion (45% in the pre-referral period to 68% in the post-referral period) of patients used ranitidine for 31–100 days, but this was lower (11–56% across referral periods) in the other databases. In all databases, the majority of individuals received ranitidine in accordance with the WHO's recommended dose (i.e. PDD/DDD of 1). Parenteral ranitidine use was low in all databases (< 5% of total ranitidine use). Although the indications for ranitidine use were missing for nearly 85% of new users, available data showed that ranitidine was mostly prescribed for GERD or gastritis without *H. pylori* (Supplemental Table 4). There were no differences in the type of indication between periods. However, there were differences in the type of indications between databases, with LPD Belgium, LPD France, DA Germany, and IMRD (UK) having the highest proportions for treatment of gastritis without *H. pylori*, and SIDIAP (Spain) and IPCI (the Netherlands) having the highest proportion for treatment of GERD (Supplemental Table 4).

3.1 Incidence of Ranitidine and Alternative Medicines Use

The incidence of the use of ranitidine, other H_2RAs, PPIs, and antacids is presented in Table 1. In the pre-referral

Table 1 Incidence rate of ranitidine and alternative medicines use by referral period

Ingredient	Period	Incidence rate per 1000 PY (95% CI)					
		DA Germany	IPCI	LPD Belgium	LPD France	SIDIAP	IMRD (UK)
Ranitidine	Pre-referral	0.77 (0.76–0.78)	4.51 (4.42–4.59)	9.03 (8.83–9.24)	1.06 (1.03–1.08)	5.85 (5.81–5.89)	8.23 (8.17–8.30)
	Referral	0.27 (0.25–0.28)	1.19 (1.12–1.27)	3.75 (3.51–4.00)	0.46 (0.44–0.49)	1.16 (1.12–1.19)	3.64 (3.56–3.73)
	Post-referral	0.06 (0.06–0.07)	0.37 (0.35–0.4)	0.10 (0.08–0.13)	0.11 (0.1–0.12)	0 (0–0)	0.31 (0.30–0.33)
H_2RAs (no ranitidine)	Pre-referral	0.04 (0.03–0.04)	0.07 (0.06–0.08)	0.03 (0.02–0.04)	0.12 (0.12–0.13)	0.08 (0.08–0.09)	0.06 (0.06–0.07)
	Referral	0.30 (0.29–0.32)	1.92 (1.82–2.02)	0 (0–0.02)	0.27 (0.25–0.29)	3.27 (3.21–3.33)	1.18 (1.13–1.23)
	Post-referral	0.18 (0.17–0.18)	1.49 (1.44–1.53)	0 (0–0)	0.17 (0.16–0.18)	1.57 (1.55–1.59)	1.98 (1.94–2.02)
PPI	Pre-referral	22.02 (21.95–22.08)	44.55 (44.3–44.81)	55.66 (55.17–56.15)	46.95 (46.81–47.1)	56.62 (56.49–56.76)	43.14 (42.98–43.29)
	Referral	27.19 (27.05–27.33)	49.72 (49.23–50.21)	69.98 (68.97–70.99)	51.34 (51.05–51.64)	61.45 (61.2–61.7)	51.60 (51.28–51.93)
	Post-referral	28.11 (28.03–28.20)	41.02 (40.78–41.26)	63.21 (62.68–63.75)	52.29 (52.12–52.47)	51.49 (51.37–51.62)	46.28 (46.09–46.46)
Antacids	Pre-referral	0.34 (0.33–0.35)	12.46 (12.33–12.6)	9.18 (8.98–9.38)	2.80 (2.76–2.84)	8.18 (8.13–8.24)	12.09 (12.01–12.18)
	Referral	0.53 (0.51–0.55)	13.34 (13.08–13.6)	10.93 (10.53–11.35)	3.41 (3.34–3.49)	7.98 (7.89–8.07)	12.87 (12.7–13.04)
	Post-referral	0.53 (0.52–0.54)	10.97 (10.85–11.1)	10.19 (9.97–10.42)	3.24 (3.20–3.29)	8.05 (8.00–8.10)	12.43 (12.34–12.53)

Pre-referral period = September 2017–August 2019; referral period = September 2019–March 2020; post-referral period = April 2020–March 2022

CI confidence interval, *DA* Disease Analyser, *H_2RA* histamine H_2-receptor antagonist, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *PPI* proton-pump inhibitor, *PY* person years, *SIDIAP* Information System for Research in Primary Care

period, ranitidine was one of the most commonly prescribed H_2-receptor antagonists, with incidence rates ranging from 0.8 to 9.0/1000 PY. There were notable variations in the incidence rates across databases. LPD Belgium (9.9/1000 PY) and IMRD (UK) (8.2/1000 PY) had relatively higher rates compared to LPD France (1.1/1000 PY) and DA Germany (0.7/1000 PY). In the referral period, there was a steep decrease of incident rate to 0.3–3.8/1000 PY, eventually dropping to 0.0–0.4/1000 PY in the post-referral period. In general, the incident use of ranitidine decreased over time (referral period and calendar year), as depicted in Fig. 1 and Supplemental Tables 5 and 6 (see the electronic supplementary material).

In comparison to ranitidine, the use of other H_2RAs such as cimetidine and famotidine was small and increased over time, with demonstrable trends in the IPCI (the Netherlands), SIDIAP (Spain), and IMRD (UK) databases (Fig. 2 and Supplemental Tables 5 and 6). PPIs, particularly omeprazole and pantoprazole, were the most commonly prescribed alternative medicine, with incidence rates ranging from 22.0 to 56.6/1000 PY in the pre-referral period, 27.2 to 70.0/1000 PY during referral, and 28.1 to 63.2/1000 PY in the post-referral period (Table 1 and Supplemental Table 5).

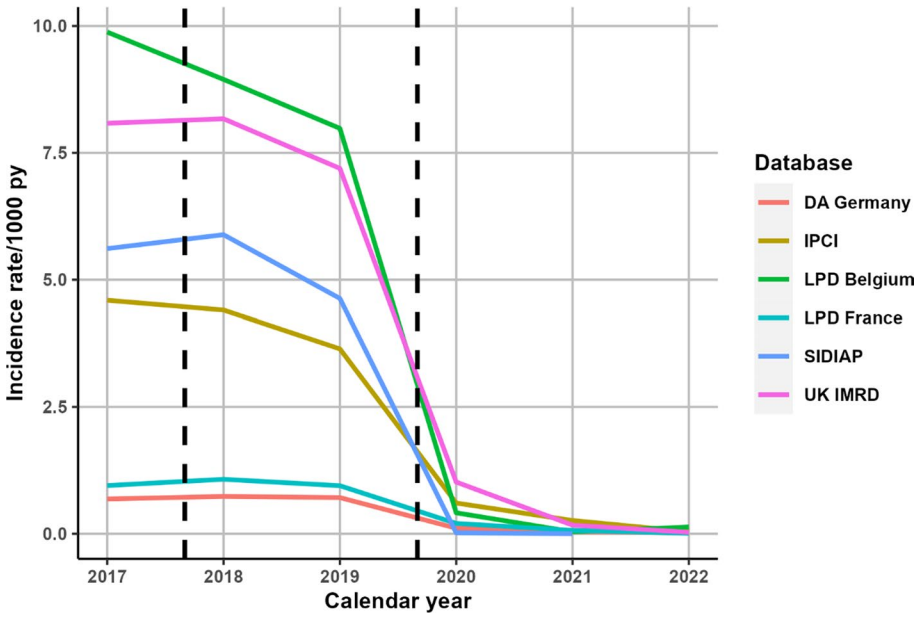

Fig. 1 Incidence rate trends of ranitidine use by calendar year. Vertical dashed lines indicate referral initiation and finalisation. *DA* Disease Analyser, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *py* person years, *SIDIAP* Information System for Research in Primary Care

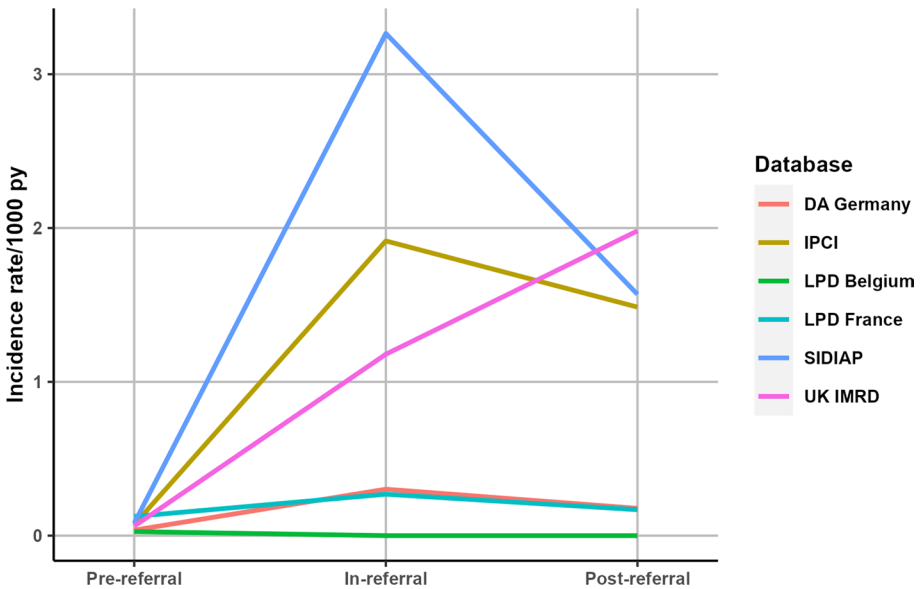

Fig. 2 Incidence rate patterns of other H_2RA use by referral period. *DA* Disease Analyser, *H_2RA* histamine H_2-receptor antagonist, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *py* person years, *SIDIAP* Information System for Research in Primary Care

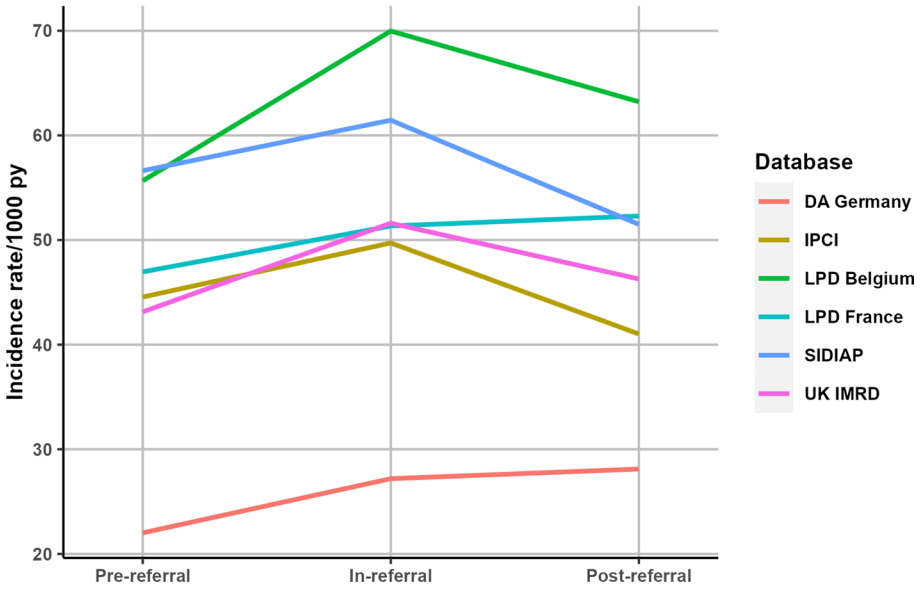

Fig. 3 Incidence rate patterns of PPI use by referral period. *DA* Disease Analyser, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *PPI* proton-pump inhibitor, *py* person years, *SIDIAP* Information System for Research in Primary Care

The incident use of PPIs increased over time in LPD France, LPD Belgium, and DA Germany, but remained stable in the other databases (Fig. 3 and Supplemental Table 6). The incidence rates of antacids ranged from 0.3 to 13.3/1000 PY throughout the observation periods, with the lowest rates in DA Germany (0.3–0.8/1000 PY) and highest rates in IMRD (UK) (12.0–13.0/1000 PY) (Supplemental Table 6). The use of antacids was stable or decreased in IPCI (the Netherlands) and IMRD (UK), but increased in LPD Belgium, DA France, SIDIAP (Spain), and DA Germany (Table 1, Supplemental Figure 1, and Supplemental Table 6). In addition, the use of prostaglandins, combination therapy for *H. pylori* eradication, and other drugs for the treatment of peptic ulcers or GERD in all databases was low (i.e. incident drug use of ≤ 5.0/1000 PY) (Supplemental Tables 5 and 6).

3.1.1 Switching from Ranitidine to Proton-Pump Inhibitors (PPIs)

The trend of early switching from ranitidine to PPIs demonstrated a gradual rise from 2017 to 2019, with rates ranging from 80 (SIDIAP) to 289 (IPCI) per 1000 ranitidine users (Fig. 4). This upward trajectory peaked in 2020, with rates ranging from 234 (SIDIAP) to 684 (IPCI) per 1000 ranitidine users. However, there was a decline in early switching in 2021–2022, with rates ranging from 0 (SIDIAP) to 336 (IPCI) per 1000 ranitidine users. An intriguing exception was observed in the IMRD (UK), which displayed a consistent and gradual increase in switching throughout the study period (177 per 1000 ranitidine users in 2017 to 609–686 per 1000 ranitidine users in 2021/2022).

A similar increasing trend was observed for late switching from ranitidine to PPIs across various databases between 2017 and 2019, with rates ranging from 141 (LPD Belgium) to 400 (SIDIAP) per 1000 ranitidine users. This upward trend reached its peak in 2020/2021, with rates ranging from 446/408 (LPD France/IPCI) to 950/1826 (SIDIAP/LPD Belgium) per 1000 ranitidine users. However, a subsequent decline occurred in 2022, with rates ranging from 140 (LPD Belgium) to 532 (LPD France) per 1000 ranitidine users.

Overall, the incidence of late switching to PPIs exceeded that of early switching, nearly reaching 100% in LPD Belgium and SIDIAP in 2021 (Supplemental Figure 2; see the electronic supplementary material). After 2021, the frequency of switching decreased or remained stable.

3.1.2 Switching from Ranitidine to Histamine H_2-Receptor Antagonists (H_2RAs)

The frequency of individuals switching from ranitidine to other H_2RAs was less evident or minimal between 2017 and 2018 (≤ 1 per 1000 ranitidine users) (Fig. 4). In 2019, switching rates saw a slight uptick across various databases, ranging from 7 (UK IMRD) to 34 (IPCI) per 1000 ranitidine users. Subsequently, a substantial surge occurred in 2020 and 2021, ranging from 31 (LPD France) to 148 (UK IMRD) per 1000 ranitidine users. However, a steep decline was observed in 2022, with rates ranging from 0 (SIDIAP/LPD France) to 56 (IPCI) per 1000 ranitidine users. A remarkable trend emerged in the IMRD (UK), showing a consistent and gradual rise in switching from 1 per 1000 ranitidine users in 2017/2018 to 112–148 per 1000 ranitidine users in 2021/2022.

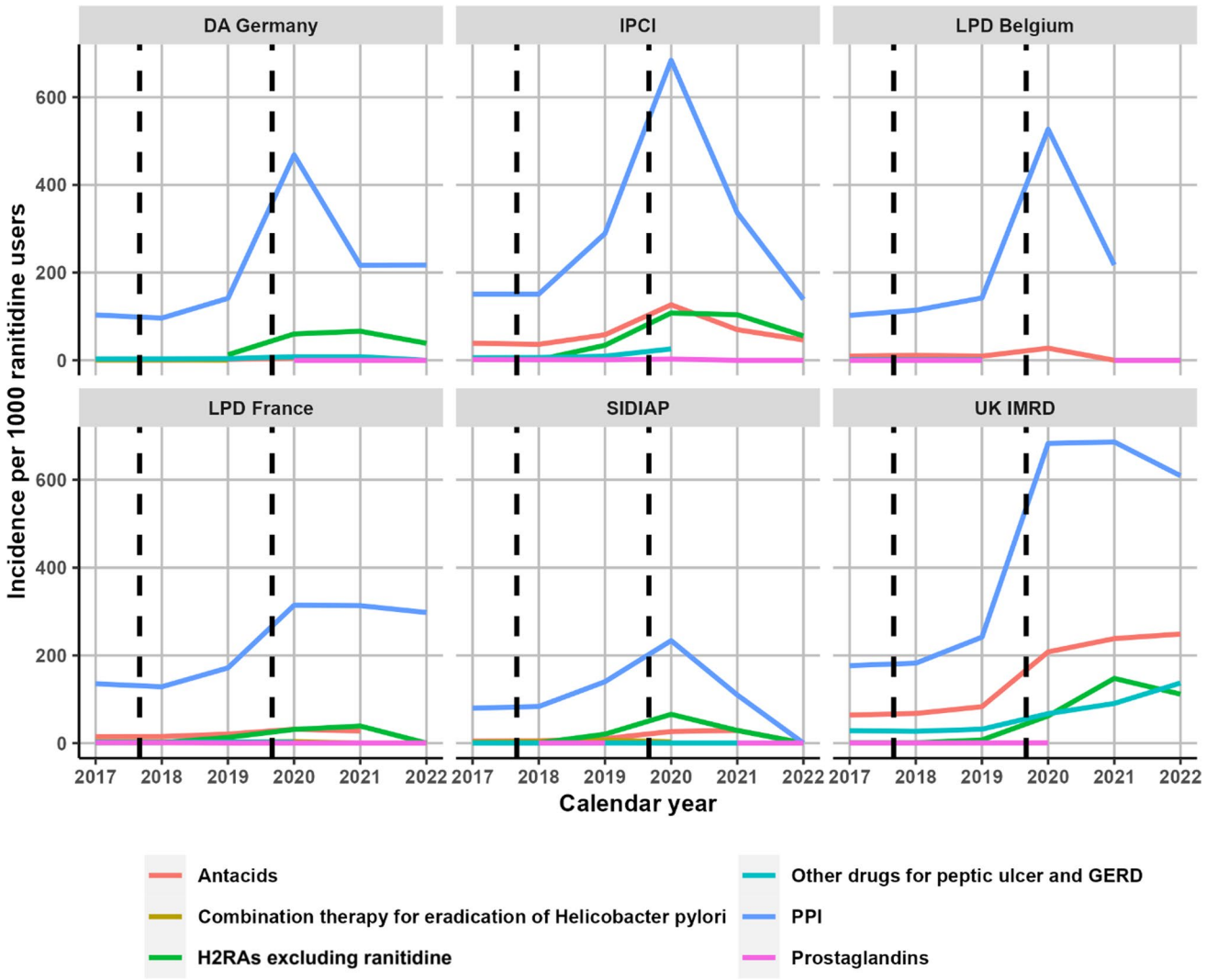

Fig. 4 Incidence rate patterns of early switching (within 90 days) from ranitidine use to alternative medicine use. Vertical dashed lines indicate referral initiation and finalisation. *DA* Disease Analyser, *GERD* gastro-oesophageal reflux disease, H_2-receptor antagonists (excluding Ranitidine), *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *PPI* proton-pump inhibitor, *SIDIAP* Information System for Research in Primary Care

3.1.3 Switching from Ranitidine to Other Alternative Medications

Early switching from ranitidine to alternative medicines increased over time, peaking between 2019 and 2020 before declining (Fig. 4). Notably, switching to antacids was most common in IPCI (the Netherlands) and IMRD (UK), albeit at a much lower rate compared to switching to PPIs. Late switching to alternative medicines, aside from PPIs, occurred in less than 30% of ranitidine users and mainly consisted of antacids, other H_2RAs, and other drugs for peptic ulcer or GERD treatment.

3.2 Incidence of Discontinuation in Individuals Treated with Ranitidine

Except for SIDIAP, which showed a sharp increase in the incidence of discontinuation from 2018 onwards, the rate of discontinuation of ranitidine therapy remained relatively stable between 2017 and 2018, fluctuated from 2019 to 2020, and then decreased from 2021 onwards (Fig. 5). The incidence of ranitidine discontinuation was comparable in 2017 for LPD Belgium, LPD France, DA Germany, and IPCI (the Netherlands), ranging from 450 to 627/1000 users, except for IMRD (UK), which had the lowest incidence in that period (i.e. 308/1000 users).

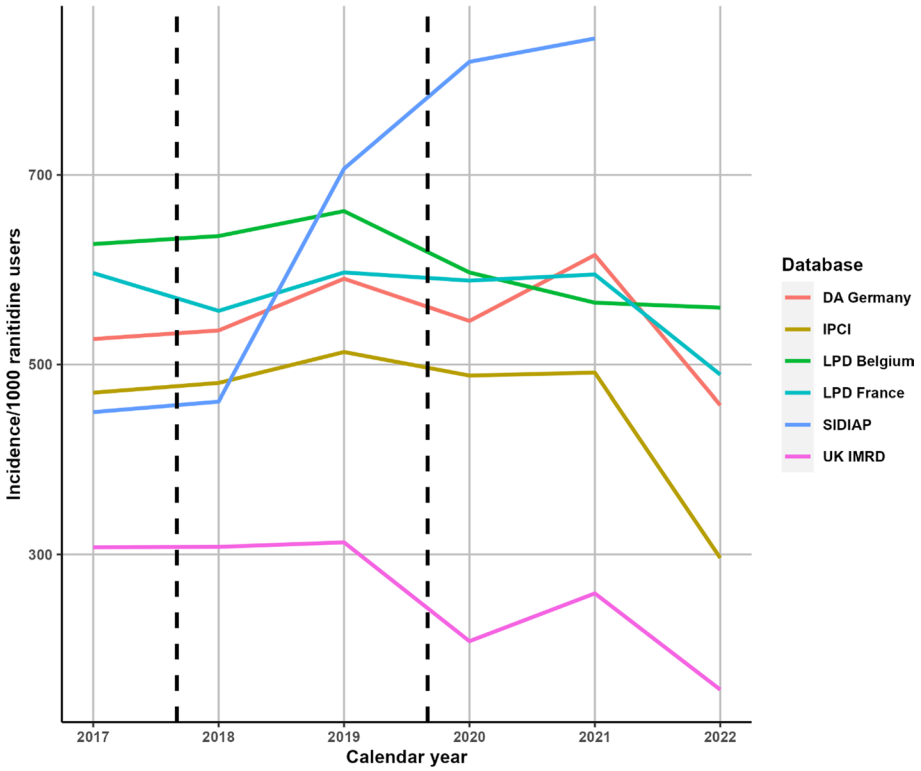

Fig. 5 Incidence rate patterns of discontinuation of ranitidine use (gap of more than 90 days). Vertical dashed lines indicate referral initiation and finalisation. *DA* Disease Analyser, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *SIDIAP* Information System for Research in Primary Care

3.3 Ranitidine and Alternative Medicines Prescription Rates by Indication

The incidence of medication use in individuals with new indications for ranitidine or alternative medicines use are listed in Supplemental Table 7 (see the electronic supplementary material). In all databases, PPIs were primarily prescribed to newly diagnosed patients with any of the conditions of interest, with incidence rates ranging from 346.0–809.0/1000 PY in 2017 to 126.0–525.0/1000 PY in 2022. Ranitidine was prescribed at much lower rates in 2017 (19.0–195.0/1000 PY), with incidence rates dropping nearly to zero in 2022. The use of other drugs, such as antacids, prostaglandins, and drugs used to eradicate *H. pylori*, was much lower. The incidence rate patterns of ranitidine prescription in individuals newly diagnosed with conditions for which ranitidine or alternative drugs are indicated are demonstrated in Fig. 6.

4 Discussion

In this multinational drug utilisation study involving 45 million individuals from six European countries, we found that ranitidine was the most commonly used H_2RA for the management of gastrointestinal complaints in the pre-referral period, but its use decreased substantially in both the in-referral and post-referral periods, with most patients switching to PPIs. Our findings reflect the potential effect of regulatory interventions on ranitidine use and are largely consistent across the included databases. Additionally, ranitidine was mostly used orally mainly for the indication of gastritis without *H. pylori* or GERD.

Our findings corroborate previous research indicating that whilst ranitidine has been commonly prescribed prior to the referral period [9, 10], its use has continued to reduce, with a consequent increase in PPI use, possibly due to their perceived differences in effectiveness in treating common gastrointestinal conditions. [10, 11] For example, Martin et al. investigated trends in PPI and H_2RA prescribing in primary care using a postal survey sent to 250 primary care physicians in the UK between 1991 and 1996. The authors not only reported a significant increase in the use of PPIs at the expense of H_2RAs, but also stated that H_2RAs were more frequently discontinued than PPIs due to treatment failure [11].

Also other observational drug utilisation studies indicated a trend towards increased utilisation of PPIs [12, 13]. A study assessing the utilisation and prescribing patterns of PPIs in ambulatory care in Scotland using the prescription costs analysis database reported a more than threefold increase in PPI prescription between 2001 and 2017 [12]. Another study describing the real-world use of PPIs in Iceland based on the national drug registry database observed an increased use of PPI from 3.5 million dispensed units in 2003 to 10.7 million dispensed units in 2015, with an

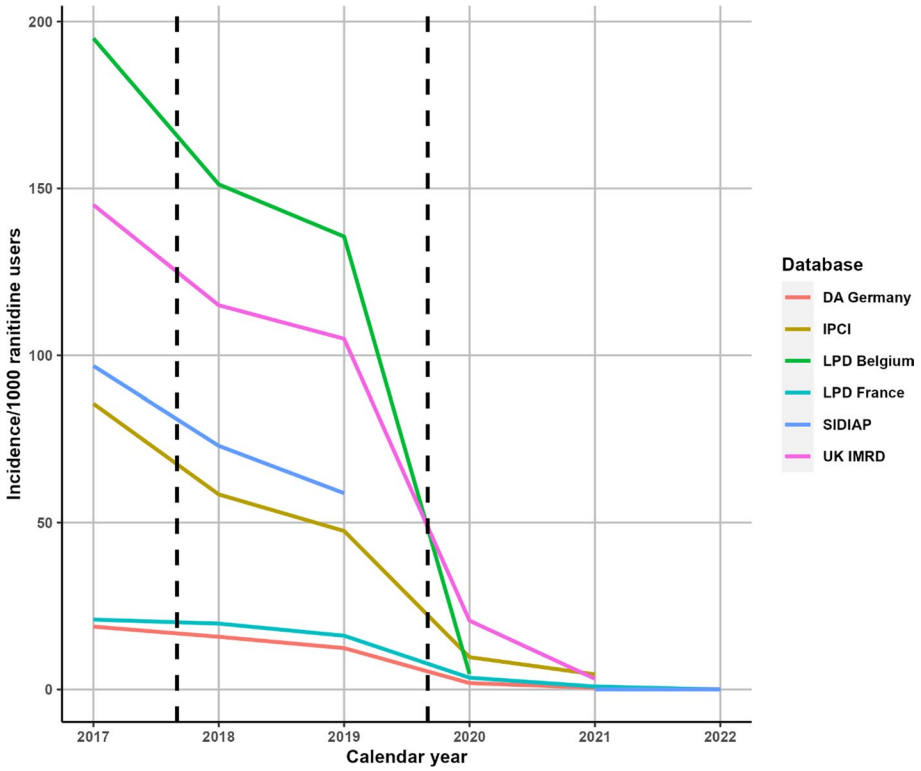

Fig. 6 Incidence rate patterns of ranitidine prescription in individuals newly diagnosed with conditions for which ranitidine or alternative drugs are indicated. Vertical dashed lines indicate referral initiation and finalisation. *DA* Disease Analyser, *IMRD* IQVIA Medical Research Data, *IPCI* Integrated Primary Care Information, *LPD* Longitudinal Patient Database, *SIDIAP* Information System for Research in Primary Care

estimated incidence rate of 33–41 per 1000 persons in 2005 and 2015, respectively, similar to the pre-referral incidence rate of PPI use in our study (22–57/1000 PY).

In the present study, switching to other H_2RAs was also observed, but at a much lower rate than switching to PPIs. This switching pattern was more discernible in countries such as the Netherlands and the UK, where a decrease in ranitidine prescriptions was offset by an increased availability of other H_2RAs. For example, a recent study of prescription datasets in primary care practices in the UK reported a 97% drop in ranitidine use in 2020, which was counterpoised by an increase in the use of other H_2RAs such as famotidine and cimetidine [14]. Notably, the proportions of switching to PPIs in our study population almost reached 100% in Spain and Belgium, implying that alternative H_2RAs, those other than ranitidine, may be scarce in these countries. For instance, in Belgium there were no alternative H_2RAs available, which was a concern for patients who require a premedication regimen to reduce the risk of hypersensitivity reactions to a variety of chemotherapy [15].

In summary, the drop in ranitidine use and subsequent increase in PPI prescription had been reported prior to regulatory actions, which were driven mainly by effectiveness amongst other factors [10, 11]. However, the recent referral by regulatory agencies undoubtedly further contributed to the sustained decline and discontinuation of ranitidine use in many European countries, as evidenced by the nearly zero incidence rates of ranitidine use in the current study. Our findings indicate that ranitidine use is mostly in line with current recommendations. Nevertheless, a continuous supply of other H_2RAs is required to ensure the availability of essential medicines for patient care, especially for indications where there is no better alternative than H_2RAs, such as for the prevention of hypersensitivity reactions in patients treated with chemotherapy.

Our study has several strengths. The generalisability of our findings is high given that we used real-world data to investigate treatment patterns of ranitidine and its alternative medicines. Additionally, we used large datasets from multiple countries, with source data mapped to the OMOP CDM, allowing us to optimise our research and obtain data in a timely and efficient manner. Despite some country-specific variations in the present study, there are several consistent findings regarding the characteristics of ranitidine users as well as similar use patterns—decreasing trends in ranitidine use throughout the study period and an increase in PPI use in the in-referral period, which stabilised or decreased in the post-referral period. However, our study has some limitations. There may be differences in the availability of certain data between databases because we used real-world data from electronic healthcare records from different countries. Although ranitidine was accessible OTC in the countries included, data on its OTC use were not available in the databases. Therefore, there is a possibility of underreporting of ranitidine use as well as the use of OTC alternatives such as antacids, low-dose H_2RAs, and PPIs. Furthermore, given that prescription records are not automatically linked to the

indication of use, we observed that the indication of use, including off-label use, was missing in up to 85% of ranitidine users (this proportion decreased to 75% when the look-back period was extended to 1 year). Since we used prescription and dispensing data, we may have overestimated the use of ranitidine and other H_2RAs given that the actual medication intake might be lower. Lastly, we included only primary care databases in our study; thus, data on the utilisation pattern of ranitidine and its alternative medicines in the hospital setting are lacking.

5 Conclusion

Regulatory recommendations and referral seem to have influenced the use patterns of ranitidine and its alternatives, favouring a switch to PPI for similar indications. This observation not only underscores the healthcare sector's ability to respond to evolving safety considerations, but also emphasises the substantial influence of regulatory interventions on clinical practice and therapeutic decisions.

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Declarations

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Conflicts of interest/competing interests The authors, Johnmary T. Arinze, Maria A.J. de Ridder, Dina Vojinovic, Hanne van Ballegooijen, Emanuil Marko, Talita Duarte-Salles, Peter Rijnbeek, and Katia M. C. Verhamme, declare no conflicts of interest directly relevant to the content of this article. This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Ethical approval The study protocol was reviewed by the institutional review boards (IRBs) of the respective databases. Given the non-interventional and observational nature of the study, ethical approval was not required for LPD Belgium, DA Germany, and LPD France. Ethical approval was granted for this study by the Scientific Review Committee (21SRC063) of IMRD (UK), the IPCI Review Board (Registration no. 8/2021) of IPCI Netherlands, and the Ethical Committee for Investigation of Medications (Code IEC: 21/272-P) of SIDIAP Spain.

Consent to participate Informed consent was unnecessary as the study used only electronic health medical records, which had been de-identified prior to data access.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

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