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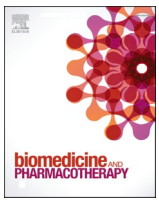

Relevance of early management by proton-pump inhibitor in acute upper gastro-intestinal tract disorder: A scoping review

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ABSTRACT

Background: Proton-pump inhibitors (PPI) are frequently used in the emergency and general practice settings in several clinical presentations linked to acute upper gastro-intestinal tract disorders as abdominal or chest pain without recommendations.
Objective: The aim of this scoping review was to assess pain reduction, diagnostic performance, and safety in the first 24 h-management in primary care or emergency medicine.
Methods: Search was realized by 2 independent reviewers in PubMed, Embase, and Web of Science following PRISMA-ScR guidelines. Only original articles or systematic reviews in English were included. Studies about chronic and/or bleeding conditions, therapeutic cocktails and studies without pain evaluation were excluded. Two methodologies were used for bias estimation.
Results: From 4442 titles, 79 full-text articles were assessed, and 9 were included. There is no strong evidence supporting the use of PPI as a first line analgesic or diagnostic test in acute syndromes linked to acute upper gastro-intestinal tract disorder. A small effect in pain reduction was retrieved in patients with low pain scores. A poor additional value in patients with gastric reflux, and a low specificity compared to other diagnostic tests were observed. A short-term PPI administration appears to be safe with low risk of serious allergic reactions, and poor adverse effects (moderate evidence).
Conclusion: Although PPIs may contribute to the multimodal analgesia in acute settings, with few and/or minor side effects, no recommendation can be drawn for their use as a primary analgesic. Data regarding the relevance of the PPI test are much less clear, no data regarding care pathways are available.

1. Introduction

Today, proton pump inhibitors (PPIs) are among the most commonly prescribed drugs [1]. Due to their good risk-benefit balance, they are among the most prescribed drugs in the world [1]. PPIs are prescribed for patients with an array of gastroenterological conditions [2]. PPIs, prodrugs, activated by gastric content, act irreversibly on the H+ ,K+ -ATPase pump, thereby blocking acid secretion. The onset of action is less than 1 h but the time required to reach the maximum plasma concentration varies from 1 h to 5 h depending on the PPI type, the diet and the age [3]. Three days can be necessary to achieve steady state inhibition of acid secretion [4].

Long-term PPI therapy is indicated, with a clear positive risk-benefit balance, for the prevention of nonsteroidal anti-inflammatory drug-induced ulcers, refractory GERD, Barrett's esophagus, severe esophagitis, chronic idiopathic ulcers, pathological hypersecretions (Zollinger-Ellison syndrome)[5]. In acute and severe conditions, PPIs are effective to shorten acute bleeding linked to digestive ulcers. But their use is not

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limited to this indication. PPIs are used to relieve dyspeptic pain but also to differentiate painful symptoms in epigastric and chest area, which may be associated with dyspeptic disorders or ulcer [6]. Their first prescription is a cornerstone that can lead to a long-term consumption. In both primary care and gastroenterology clinics where patients are often prescribed PPIs, unnecessary chronic use often occurs due to ease of access, simplicity of administration and low price [7].

In the Emergency department (ED) and in general practice, it is recommended to manage pain on the basis of etiological treatment to avoid opioid misuse (inappropriate initial prescription and continuation)[8]; including abdominal pain management [9]. Diagnosis of acute abdominal pain at first presentation is difficult despite its high prevalence [10]. The low specificity of the clinical signs is a hindrance, particularly in women presenting for epigastric pain [11,12]. The final diagnosis of "non-specific abdominal pain" accounted for more than one third of cases. The large majority of these patients remain as outpatients, with instructions and prescriptions for waiting treatments at discharge of the ED [13]. Misuse is a risk [14].

On the other side, chest pain is a common polymorphous syndrome representing 1.5% of consultations in primary care [15]. Non-specific, clinical symptoms in the chest area may be associated with cardiac, vascular, gastrointestinal, pulmonary and other diseases. In particular, in the ED, approximately 60–90% of patients with chest pain present non-cardiovascular chest pain (NCCP) [16] neither other serious conditions. After ruling out coronary threat, diagnosis is not always obvious, and etiological therapeutic tests are regularly performed using pain relief as judgment criteria (as aspirin in pericarditis). Several studies demonstrated that approximately 30% of NCCP patients had abnormal esophageal manometry [17–19]. Immediate PPIs'analgesic efficacy could help to determine gastrointestinal etiologies. Endoscopic diagnoses for upper gastro-intestinal tract disorders are robust but not applicable in a routine procedure in the first 24 h management.

However, few reports target short-terms effects of PPI administration in the ED or in general practice. A recent meta-analysis, reported an acceptable sensitivity and specificity regarding diagnostic approach toward NCCP but without clear judgment criteria in the first 24 h-management [20]. Most studies target long-term effects (days to years), are conducted during a "gastroenterology pathway" [21], are based on repeated clinical assessment by dyspepsia scores, compare the appropriateness of this approach to endoscopic follow-up and, focus on long-term safety [22–24].

Until now, the data on the clinical relevance, efficacy and safety of PPI administration in acute settings such as EDs or general practice, are scarce. This scoping review aims to discuss the place of PPI in acute upper gastrointestinal disorders as an immediate safe pain-reducing agent and/or as a diagnostic test in primary care setting or in ED.

2. Methods

A scoping review was performed [25,26] following the Preferred Reporting Items for Systematic reviews and Meta-analyses for scoping review (PRISMA-ScR) criteria [27] (Supplementary Table 1).

2.1. Identification of research questions

Research questions were: "Can PPIs be used in primary care or in ED as pain killers in case of acute abdominal pain?", "Can PPIs be used safely?", "Can PPI prescription be used as a diagnostic test for peptic diseases?". The PICO question was: In patients suffering from pain in the ED or visiting their general practitioner (P), how does PPI (I) compared to other analgesics or placebo (C) safely influence pain reduction and diagnostic performance in 24 h (O)?

2.2. Selection of publications

Electronic research was organized in Pubmed, Embase and Web of science in December 2022. The following search terms were used: ("proton-pump inhibitor" OR "omeprazole" OR "pantoprazole" OR "esomeprazole" OR "lansoprazole" OR "rabeprazole" OR "dexlansoprazole") AND ("emergency department" OR "emergency services" OR "primary care" OR "emergency medicine" OR "ambulatory" OR "outpatient" OR "primary care physicians" OR "short-stay in-patient unit") AND ("pain" OR "abdominal" OR "acute" OR "gastritis" OR "pancreatitis" OR "peptic ulcer" OR "peptic disease" OR "gastro duodenal" OR "undifferentiated abdominal pain").

The inclusion criteria were: (i) publications in English; (ii) human studies. The exclusion criteria were: (i) evaluation of PPIs with synergic drugs as experimental treatment, (ii) no judgment criteria related to pain relief before 24 h and (iii) critical care and, (iv) chronic pain (v) post-operative, (vi) peri-operative (vi) gastro-enterology services, (vi) renal colic, (vii) bleeding and (viii) case reports, congress abstracts, recommendation texts or commentaries.

Two reviewers (VE.L. and F.C.) screened the publications based on titles and abstracts. After, they evaluated full-text for inclusion. In case of discrepancy, at each step, they discussed until they reached a consensus.

2.3. Extraction of data, summary of results and evaluation of the quality

For each publication included, the main data were extracted. The study design, the population, the objectives, the results, the conclusions and the level of evidence [5] were evaluated. The quality of included study were evaluated by the two reviewers ((VE.L. and F.C.).) using the National Institutes of Health's study quality assessment tools [28] and the GRADE process [29,30].

3. Results

3.1. Selection of articles included

From database searches, 4898 papers were identified. After removing the duplicates, 4492 were screened at the title and abstract levels and 79 articles were retained for full-text assessments. Finally, 9 articles met the inclusion criteria and were included. The flowchart is presented in Fig. 1.

3.2. Characteristics of articles included

The main findings of included studies are summarized in Table 1. Among the 9 included articles, from 2002 to 2019, there were 3 randomized controlled trials (RCT) [6,31,32], 2 prospective observational studies [33,34], 2 retrospectives observational studies [35,36], 1 professional practice evaluation [37] and 1 systematic review and meta-analysis [38]. Most of the studies were monocentric [6,31,32,35,36]. Regarding original studies, 3 studies occurred in Asia [6,31,32], 2 in North of America [33,37] and 3 in Europe [34–36].

Most patients were outpatients. Four studies took place in the ED [6,31,32,35] whereas 3 studies involved patients presenting to a general practitioner [33,34,37]. Patients had different symptoms: heartburn, epigastric pain, or both, isolated or associated with other elements of the dyspeptic syndrome. Patients had suspected upper gastro-intestinal diagnoses in context of chest-pain syndrome, or acute abdominal crisis, either assessed diagnosis of gastroesophageal reflux disease (GERD) or proven peptic ulcer.

Several drugs were analyzed: Pantoprazole [6,31,32,36–38], Esomeprazole [34], Omeprazole [38], Lansoprazole [38], Rabeprazole [38]. In 2 studies, the nonspecific term PPI was used [33,35]. PPIs were mostly compared to Ranitidine [31,32].

Several therapeutic schemes were described. Pantoprazole was administered by a single intravenous (IV) dose [6,31,32], or by oral administration [34,37]. IV could be a long infusion (2–4 h)[32] or rapid infusion (2–4 min)[31]. In case of oral administration, the prescription

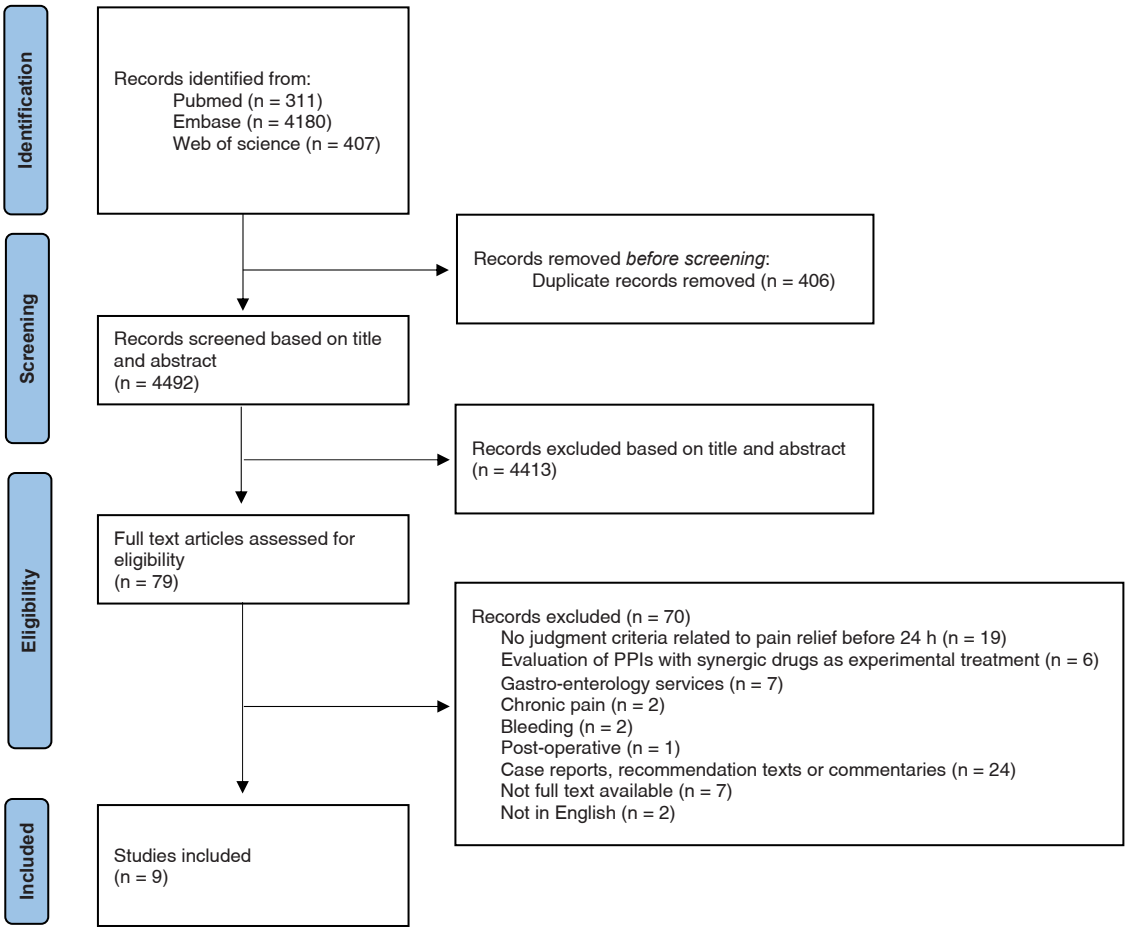

Fig. 1. Flowchart of the scoping review.

lasted several days [34,37].

3.3. Synthesis of the results

3.3.1. Use of proton-pump inhibitor as a pain killer

Three RCTs investigated the efficacy of PPIs as pain killer in the ED for suspected upper gastro-intestinal tract disorders, within 24 h of admission [6,31,32]. One observational study analyzed PPIs effect in primary care [37].

Senay et al. [31] compared the effectiveness of Pantoprazole and Ranitidine in patients suffering from dyspeptic symptoms with a Visual Analogue Scale (VAS) $\geq$ 20 mm. Thirty-three patients received a 2–4 min intravenous infusion of 40 mg Pantoprazole and 33 other patients received a 2–4 min intravenous infusion of 50 mg Ranitidine. The pain was effectively reduced at 30 and 60 min in both groups but without significant difference between groups. However, 24.2 à 39.4% of rescue rates were observed indicating additional treatments at 60 min despite pain reduction, higher in the Pantoprazole group but without statistical difference. Rescue drugs were not mentioned.

Khatir et al. [32] focused on patients with complaints of epigastric pain in a context of early diagnosis of dyspepsia and with VAS $\geq$ 20 mm. Fifty patients were treated with a 2–4 h intravenous infusion of 40 mg Pantoprazole and 50 patients were treated with a 2–4 h intravenous infusion of 50 mg Ranitidine. Both treatments significantly decreased the pain score at 30 and 60 min. Ranitidine was significantly more effective ($P < 0.001$).

Musikatavorn et al. [6] evaluated the immediate effect of intravenous Pantoprazole in addition to "the conventional gastrointestinal cocktail" (30 mL of open-labeled antacid containing 1.32 g of aluminum hydroxide, 0.72 g of magnesium hydroxide and 20 mg of hyoscine butylbromide) in patients suffering from severe dyspeptic pain (either heartburn or epigastric pain as VAS $\geq$ 50). Forty-three patients were treated with 80 mg of intravenous Pantoprazole and 44 patients received 10 mL of placebo. The mean 60-min VAS scores were similar between the two groups. There was no significative statistical difference in terms of rate of "responders," additional drug use, adverse effects, and patient satisfaction.

Armstrong et al. [37] examined the efficacy of daily oral Pantoprazole 40 mg in patients with upper gastrointestinal dyspeptic symptoms (heartburn and epigastric pain). Results from questionnaires and daily symptom diaries of 3261 primary care patients led to conclude that symptom severity scores (assessed with a 5-point likert scale) decreased from day one.

3.3.2. Prescription of proton-pump inhibitors as a diagnostic test

Four studies analyzed PPI prescription as a diagnostic test for peptic diseases [33–35,38].

Two studies focused on NCCP. Regarding general practice, PPI test was prescribed in 45% of cases [33] whereas, in ED, it was prescribed in 20% of total cases and in 71.4% of cases of gastrointestinal disease [35]. In the ED, this prescription was not followed by recommendations about a further follow-up assessment of PPI effect (7%). Among the 71.4% with gastrointestinal chest-pain receiving a PPI, 2% received PPI only at presentation, whereas 37% at discharge, and 28% both [35].

Two studies included isolated upper gastro-intestinal disorders. In a systematic review and meta-analysis, Zhang et al., analyzed the effect of PPI test and compared it to GERDQ questionnaire, baseline impedance, mucosal impedance, dilated intercellular spaces, salivary pepsin and

Table 1
Characteristics and main findings of included studies.

Author, Year, Country	Design Duration	Setting	N	Population	Treatment / Test	Outcomes / Main Findings
Musikatavorn et al. [6], Thailand	RCT Double blind 10 mths	ED	87	Severe reflux "heartburn" (VAS ≥ 50 mm) or dyspeptic epigastric pain 15–50 years old	Baseline (G1 and G2): GI cocktail (30 mL of open-labeled antacid (containing 1.32 g of aluminum hydroxide, 0.72 g of magnesium hydroxide) and 20 mg of IV HB). Then, 2 groups: G1: 80 mg IV pantoprazole (n = 43) G2: IV placebo (n = 44)	Primary outcome: To evaluate the immediate effect on pain score - 60-minute VAS: no difference between G1 and G2 - "Responder"[a] rate: G1 74.4% vs G2 81.8% (p = 0.40) - Minor adverse effects: G1 69.8% vs G2 70.5% (p = 0.92) - Additional drug use: G1 20.9% vs G2 25.0% (p = 0.65) Secondary outcome: Patient satisfaction at the end of the study - Patient satisfaction: G1 79.1% vs G2 77.3% (p = 0.95)
Senay et al. [31], Turkey	RCT Double blind 3 mths	ED	66	Epigastric pain suggestive of dyspepsia and VAS ≥ 20 mm ≥ 18 years old	G1: 40 mg pantoprazole, IV 2–4 min G2: 50 mg ranitidine, IV 2–4 min	To compare the effectiveness, the adverse effects, the need of rescue and the recurrence of pain of 2–4 min IV of 50 mg ranitidine or 40 mg pantoprazole - 30- and 60-minutes VAS: significantly reduced in G1 and G2, with no difference between the two groups - Rescue rates (need for additional drugs at 60 min): G1 39.4% vs G2 24.2% (p = 0.186) - No adverse effects in G1 and G2 - Recurrence of pain at 24 h after ED discharge: lower for G1 (30.0%) than G2 (41.4%) (p = 0.361)
Khatir et al. [32], Iran	RCT Double blind NA	ED	100	Epigastric pain with early diagnosis of dyspepsia and VAS ≥ 20 mm ≥ 18 years old	G1: 40 mg pantoprazole, IV 2–4 h (n = 50) G2: 50 mg ranitidine, IV 2–4 h (n = 50)	To compare the analgesic effect of 2–4 h IV injection of ranitidine or pantoprazole on epigastric pain in the ED - 30- and 60-minutes VAS: significantly reduced in G1 and G2 but ranitidine was more effective - Adverse effect symptoms: - No headache, dizziness, hypoglycemia and nausea-vomiting in G1 and G2 - Bloating was significantly higher in G1 12.5% vs G2 0% (p = 0.009)
Armstrong et al. [37], Canada	OBS PROS 20 mths	PC	726	Family physician, internists, surgeons and gastroenterologists with at least 5 patients with upper GI dyspeptic symptoms treated with PPI NA	40 mg of oral pantoprazole daily during 7 days	To assess the range of upper gastrointestinal acid-related symptoms in clinical practice and the rapidity of their response to oral pantoprazole during seven days of therapy thanks to questionnaires and a daily symptom diary - 2273 patients with isolated GERD (66.9%), peptic ulcer (9.7%). - Symptom severity scores (1–5) decreased during the seven days of treatment: - heartburn 2.59 (day 0) vs 2.04 (day 1) - epigastric pain 2.54 (day 0) vs 2.14 (day 1) - Subgroup of almost continuous symptoms: - heartburn: ≃3.5 (day 0) vs ≃2.5 (day 1) - epigastric pain: ≃3.5 (day 0) vs ≃2.8 (day 1)
Wong et al. [33], Arizona (US)	OBS 5 mths	PC	205	Physicians: general practitioners, internists, family physicians and others ≥ 30 years old	24 items questionnaire	To determine the preferences of diagnostic tests, referral patterns, and treatment plans of NCCP - Mean number of NCCP patients / physician: 108 - Diagnosis the cause of a patient with NCCP: 45.6% PPI trial - First referral pattern: gastroenterologist 16.6% - First line treatment modalities in NCCP: 37.8% PPI

(*continued on next page*)

Table 1 (*continued*)

Author, Year, Country	Design Duration	Setting	N	Population	Treatment / Test	Outcomes / Main Findings
Aanen et al. [34], Netherlands	OBS PROS Double blind 2 years	PC	74	Epigastric pain, chest pain, epigastric burning, heartburn, regurgitation, acid taste 41–62 years old	40 mg oral esomeprazole during 13 days (PPI test)	Primary outcome: To determine the diagnostic accuracy of the PPI test in a PC population using the SAP outcome as reference test. - SAP: positive[b] in 70% of the subjects - Positive predictive value with SAP as reference standard was 75% (CI 0.62–0.85) and negative predictive value 54.0% (CI 0.22–0.80) - Likelihood ratios of GERD symptoms were comparable (1.2 (CI 0.9–1.6)) - Sensitivity, specificity, positive and negative predictive value did not differ significantly for each test day, neither did the likelihood ratios differ Secondary outcome: To determine SI and SSI calculation (positive symptom-reflux association) - SI positive in 62% of the subjects - SI positive in 45% of the subjects
Wertli et al. [35], Switzerland	OBS RETRO 3 years	ED	1341	Non-cardiac chest pain $\geq$ 18 years old	PPI	To evaluate the diagnostic tests, bedside treatment recommendations and initiated treatments in patients presenting with non-cardiac chest pain to the emergency department - Diagnostic test with PPI was prescribed in 20.5% without specific recommendations at discharge (2.2%) - During the ED stay, 71.4% with gastrointestinal diseases and with chest pain received a PPI, only 5.7% at presentation, only 37.1% at discharge, and 28.6% both
Zhang et al. [38], China	SR/MA Until April 2028	NA	15289	GERD, without specific disease, without surgery, exclusion of only extraesophageal symptoms $\geq$ 18 years old English and Chinese language studies	PPI Tests (omeprazole or lansoprazole or pantoprazole or rabeprazole or esomeprazole) compared to GERD questionnaire, baseline impedance, mucosal impedance, dilated intercellular spaces, salivary pepsin, esophageal pH/pH impedance monitoring and endoscopy	To assess the diagnostic characteristics of the GERD questionnaire, PPI test, baseline impedance, mucosal impedance, dilated intercellular spaces, salivary pepsin, esophageal pH/pH impedance monitoring and endoscopy for GERD, using pairwise comparison and NMA - PPI test: complete relief of heartburn' is the most commonly adopted criteria - 2 divergent analyses: NMA and direct pairwise comparison - Direct pairwise comparison results indicated that the PPI test had the lowest specificity
Casciaro et al. [36], Italy	OBS RETRO 5 years	NA	1229	History of drug allergy and admitted to the Allergy and Clinical immunology division NA	Esomeprazole, pantoprazole, lansoprazole, omeprazole and unknown PPIs	To assess the immunoallergic safety of PPI - Positive history for hypersensitive reaction to PPI: 12 patients with GERD or gastritis - Angioedema or urticaria (11/12 patients) - Pantoprazole: most frequently PPI involved in allergic reaction (5/12 patients)

ED: Emergency department; G1: Groupe 1 IPP experimental treatment; G2: Groupe 2 comparator; GERD: Gastroesophageal reflux disease; GI: Gastro intestinal; PPI: Proton pump inhibitor; NMA: network meta-analysis; NSAID: Non-steroidal anti-inflammatory drugs; OBS: Observational study; PC: Primary care; PROS: Prospective; RCT: Randomized controlled trial; SAP: Symptom association probability; RETRO: Retrospective; SI: Symptom index; SR/MA: Systematic review and meta-analysis; SSI: Symptom sensitivity index; VAS: Visual Analogue Scale. [a]Diminution of VAS $\geqslant$ 50% in post-treatment compared to pre-treatment and VAS post-treatment $\leq$ 40 mm. [b]PPI test was considered positive when the subjects reported adequate symptom suppression. SAP takes both the total number of reflux episodes as well as the total number of symptoms into account.

esophageal pH/pH impedance monitoring/endoscopy for the diagnostic of GERD including symptoms as heartburn [38]. As the definition of positive PPI test differed among studies, they considered the test positive if there was 'complete relief of heartburn'. The authors concluded that PPIs test had the lowest specificity of all the diagnostic-tests compared. Aanen et al., in an observational study, assess the diagnostic accuracy of PPI test by 40 mg esomeprazole per os during 13 days in a primary care population as well as its additional value over reflux history, using the Symptom Association Probability (SAP) outcome during 24-h [34]. The SAP considered both the total number of reflux episodes and the total number of symptoms. The PPI test was considered positive when the subjects reported adequate symptom suppression. The SAP was positive in 70% of the subjects. The positive predictive value with SAP as reference standard was 75.0% (73.6–76.7) and the negative predictive

value with SAP 57.1% (44.1–63.6). Furthermore, the likelihood ratios of GERD symptoms were compared and were similar (1.2 (CI 0.9–1.6)) whatever the day of treatment. The study only included patients who had typical reflux symptoms and who were considered to have a high prevalence of GERD but the PPI test had too low specificity and negative predictive value to diagnose GERD in these conditions. Aanen et al. [34]. concluded that "the PPI test is unable to determine the presence or absence of GERD in a group of primary care patients and subsequently does not add any additional value to an adequate reflux history."

3.3.3. Proton-pump inhibitors safety

Three studies examined the adverse effects of short-term PPI use after emergency admission [31,32,36].

Casciaro et al. [36] investigated the allergic effect of PPIs (Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole and Esomeprazole) with a history of drug hypersensitivity. Data on PPI safety were extrapolated from a database of 1229 patients with adverse drug reactions. Twelve patients reported PPIs hypersensitivity reactions. The most common PPI was Pantoprazole. The authors concluded that, despite an increasing number of adverse drug reactions regularly under-documented, given the frequency of PPIs prescription worldwide, the risk of serious allergic events remained low.

Khatir et al. [32] compared the analgesic effect of 2–4 h infusion of 40 mg pantoprazole and 2–4 h infusion of 50 mg ranitidine in patients with epigastric pain, with early diagnosis of dyspepsia and VAS $\geq$ 20 mm. No headache, dizziness, hypoglycemia and nausea-vomiting reported in both groups. Bloating was far higher in Pantoprazole-treated patients (12% vs 0%), but already observed before treatment as a symptom of dyspeptic syndrome. Thus, the authors concluded that association between PPIs and adverse events cannot be highlighted.

Senay et al. [31] compared the effectiveness of 2–4 min infusion of 40 mg Pantoprazole and 2–4 min infusion of 50 mg Ranitidine in patients suffering from dyspeptic symptoms with a VAS $\geq$ 20 mm. In both groups, no adverse effects were observed at 30 and 60 min

3.3.4. Quality of the articles included

Risk of bias by study design is presented in Tables 2 to 4. There was a moderate risk of bias in systematic reviews (Table 2), a moderate to high risk of bias in controlled intervention studies (Table 3), and in observational studies (Table 4). In the systematic review of Zhang et al. [38], the moderate risk of bias was due to the criteria "independent rate" and "characteristics and results". In controlled intervention studies, the high risk of bias was mainly due to the criteria "similar group at baseline" and "other interventions". In observational studies, the risk of bias was most often recognized as issues with "sample size", "outcome measures" and systematically with "confounding variables".

The results of the GRADE analysis are summarized in Fig. 2. A low quality of evidence was determined for the use of PPI as a pain killer in case of acute abdominal pain suspected as relative to a dyspeptic syndrome, a very low quality of evidence for the prescription of a PPI as a diagnostic test for peptic diseases and a moderate quality of evidence for the safety of the use of PPI in acute conditions.

Table 2
Risk of bias assessment for systematic reviews and meta-analyses using the NIH quality assessment tool.

	Focused question	Eligibility criteria	Literature search strategy	Independent review	Independent rate	Characteristics and results	Bias assessed	Heterogeneity assessed
Zhang et al. [38]								

In the color-coded ranking, green color represents low risk of bias, orange some concerns, and red high risk of bias.

4. Discussion

To date, in general practice or in the ED, no recommendations are available about appropriate short-term prescriptions based on PPIs efficacy as first-line analgesics or their value as positive diagnostic tests. This scoping review aimed at determining if the PPIs reduce pain scores and/or influence diagnostic performance in the 24 h first management in primary care or emergency medicine.

4.1. Principal findings and comparison with prior work

4.1.1. Scarce and unreliable data about analgesic properties

Regarding nociceptive process, PPIs and other drugs that inhibit acid secretion are unlikely to lead to an immediate reduction in acute pain related to upper gastrointestinal tract disorders. But PPIs can modulate pain, via the placebo effect or other indirect pain control mechanisms [39,40]. Unfortunately, this scoping review revealed that scientific data are still scarce and lack robustness.

Only 4 studies were performed in the ED [6,31,32,37], on epigastric or NCCP syndrome, including one observational study [37], older than 5 years and with a low level of evidence. No study was conducted in Europe and the United States, although high prevalence of PPIs prescription in these countries [41–43].

Pantoprazole was the only drug tested in the included RCTs. This may be explained because Pantoprazole is increasingly used following recommendations highlighting its strong action on histamine receptor antagonists [44] for the treatment of gastric acid-dependent disorders. Pantoprazole was compared to Ranitidine (anti-H2 receptor inhibiting the effect of histamine in gastric wall cells and preventing acid secretion [45]) but not with placebo alone. In the only study in which patients received a placebo [6], a "gastrointestinal cocktail" known to relieve symptoms [46], was administrated to obtain a standard of care at baseline, as "pre-analgesia". In the same line, in 2 RCTs, a quarter of patients was already treated with analgesics before their arrival in the ED (20.9% [6], 25% [32]).

Most RCTs studies used VAS scale to evaluate efficacy of PPIs, which was a strength [6,31,32] but data were either clinically un-relevant or insufficient to conclude on the effectiveness of PPIs as analgesics. Inclusion criteria [31,32] based on VAS $\geq$ 20 led to mix patients with different initial pain classes without consideration of validated ranges [47] making assessment of effectiveness difficult. Some decrease are too tight [37] to lead to PPI use as a pain killer in the ED. High rescue rates at 60 min raise doubts about the reliability of some relief criteria despite use of classical VAS cut-off (<30) [31]. Non-validated tools in the ED, based on the frequency of everyday symptoms [37] cannot be currently transposed to everyday practice and used to select the appropriate analgesic.

There were weaknesses in RCTs study-designs [6,31,32]. These RCTs have at least one high risk of bias (Table 3) and one had 5 criteria of analysis coded as high risk of bias [32]. First, numerous selection bias was observed. Sample size were small, with a maximum of 100 patients (50 per arm of treatment) without precise diagnoses. GERD patients were overrepresented, while the symptomatic response rate to PPIs is known to be 36.1% in GERD patients raising to 55.5% in erosive esophagitis [48]. Depending on RCTs, the mean age differed (from 29.4 $\pm$ 9.2 years [6], to 48.9 $\pm$ 16.2 years [32]) and was concentrated in those under 50 years of age, while the onset of GERD symptoms was described in older population[49], with a higher prevalence of NCCP observed in women aged 50–60 years [50]. Patients were mostly female and sex prevalence differed between studies (81.4% [6], 60.6% [31],

Table 3
Risk of bias assessment for controlled intervention studies using the NIH quality assessment tool.

	Type of study	Method of randomization	Treatment allocation concealed	Blinded information from the	Blind evaluation	Similar group at baseline	Overall drop-out rate at	Differential drop-out rate	Adherence to the intervention	Other interventions	Outcomes assessment	Sample size	Outcomes reported / subgroups	Analyze of randomized
Musikatavorn et al. [6]														
Khatir et al. [32]														
Senay et al. [31]														

In the color-coded ranking, green color represents low risk of bias, orange some concerns, and red high risk of bias.

Table 4
Risk of bias assessment for observational studies using the NIH quality assessment tool.

	Research question	Study population	Participation rate	Recruitment	Sample size	Analyses	Timeframe	Exposures	Exposure measures	Exposure(s) assessment	Outcome measures	Blinding of outcome assessors	Loss to follow-up	Confounding variables
Aanen et al. [34]														
Wertli et al. [35]														
Casciaro et al. [36]														
Armstrong et al. [37]														
Wong et al. [33]														

In the color-coded ranking, green color represents low risk of bias, orange some concerns, and red high risk of bias.

81.3% [32], 59.2% [37]). Furthermore, in the study by Khatir et al. [32], treatment arms presented several differences: inhomogeneous symptomatology (epigastric pain fickle), a significantly higher percentage of women in the Pantoprazole group (81.3% vs. 50%) and a significant difference in long-term analgesic use (25% vs. 52.9%). Second, Pantoprazole dosage and administration scheme differed among RCTs (80 mg IV [6], 2–4 h IV of 40 mg [32], 2–4 min IV of 40 mg [31]) and deserve comment. A 2–4 h IV administration is questionable in terms of pharmacokinetic or organization. Conversely, the proposal of once daily oral administration of 40 mg [37] could be studied with an end point at 24 h.

4.1.2. An unclear specificity of PPI test and a poor strategy

The prevalence of PPI tests ranges from 45% in general practice [33] to 71% in the ED [35], and their predictive value was mainly studied for GERD, which is the most frequent esophageal etiology of NCCP representing up to 60% [51,52]. Robustness and relevance of PPI tests remains to be established in the first 24 h management of NCCP, and no data are available in isolated epigastric pain.

In the only available systematic review, PPI test presented the lowest specificity among 8 tests in heartburn patients with suspected GERD [38]. In addition, PPI tests seem to have a very low specificity and provide reliable but small values of likelihood ratios of GERD symptoms which confirmed a low clinical relevance whatever the time point of evaluation [34]. Moreover, the sensitivity and specificity of PPI test appear to be lower in 24-hour pain suggestive of GERD without a confirmed diagnosis than in a population with a confirmed diagnosis of GERD [21,34,38]. These results are consistent with the low efficacy described in non-severe esophageal disorders (non-erosive)[53] and, with the low specific diagnostic accuracy previously described in general practice in heartburn syndrome or epigastric pain [16].

Moreover, no care pathway is proposed after the ED journey. This scoping review shows that patient outcomes after a PPI test are insufficiently evaluated and connected to its result. Wertli et al.[35] conducted a study in a representative NCCP population presenting at the ED; i.e. mostly ambulatory, including 35% of gastrointestinal-linked

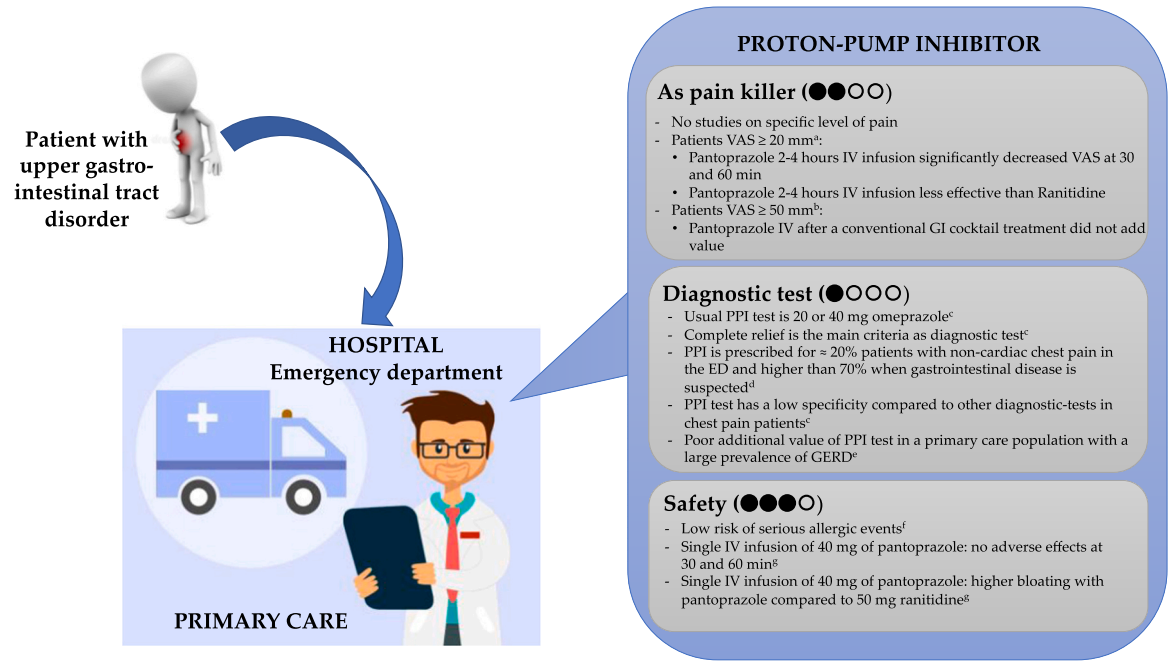

Fig. 2. Summary of the results based on the GRADE process. High (●●●●) when the true effect lies close to that of the estimate of the effect; moderate (●●●□), when the true effect is likely to be close to the estimated effect, but there is a possibility that is substantially different; low (●●□□), when true effect may be substantially different from the estimated effect; and very low (●□□□), when the true effect is likely to be substantially different from the estimated effect. ED: emergency department; IV: intravenous; PPI: proton pump inhibitor; NCCP: non-cardiac chest pain; VAS: visual analog scale.
a: Senay et al. [31]; b: Musikatavorn et al. [6]; c: Zhang et al. [38]; d: Wertli et al. [35]; e: Aanen et al. [34]; f: Casciaro et al. [36]; g: Senay et al. [31].

chest pain with 40% under long-term PPI therapy, and results confirmed the absence of a PPI treatment strategy. Prevalence of PPIs during ED journey highly differed from prevalence of PPI test and prescription rates were poorly linked with a patient past history of gastrointestinal-linked chest pain (15% of additional prescriptions). Initial PPI prescriptions in the ED appeared to be more correlated to the other pharmacological prescriptions: lower non-steroidal anti-inflammatory drugs and acetaminophen uses were observed in the gastrointestinal-linked chest pain group receiving PPIs. Finally, only one-third of patients with gastrointestinal-linked chest pain received PPI at presentation and had a prescription at discharge, and most left the ED without specific recommendations for follow-up assessment. In a recent study of 355 NCCP patients, authors demonstrated that 49% visited the ED, 42% had repeated cardiac testing, and 15% were seen by a gastroenterologist [54]. Our results are consistent with literature, and with lack of a gastrointestinal-linked chest pain pathway in ED and specific PPI management in NCCP. Thus, it may be worthwhile to separate PPI use for diagnosed erosive digestive disease from PPI use for pain suspected to be due to upper gastrointestinal tract disorder. In addition, there is no study evaluating the link between the first PPIs test and patient final outcomes (recurrencies, PPI long-term utilization, hospitalization rate, etc…). PPIs can induce achlorhydria and hypergastrinemia, causing rebound acid hypersecretion, which may paradoxically worsen GERD symptoms as dyspepsia [55].

4.1.3. A long-term safety still in the scope

Adverse effects of short-term PPI use were mainly associated with Pantoprazole and appear to be negligible. Even in patients with a history of drug hypersensitivity, PPI hypersensitivity reactions occurred in less than 10% of patients [36]. No classical side effects such as headache, dizziness, hypoglycemia, or nausea-vomiting were reported at 30 and 60 min following 2–4 min [32] or 2–4 h [31] infusion of 40 mg of Pantoprazole. Only floating, a symptom of dyspeptic syndrome, was higher in patients treated with Pantoprazole but it could be linked to the disease itself. Thus, PPI seems to be a safe therapeutic in acute abdominal pain during the first ED management or after a first consultation of a general practitioner. The safety is less insured after this first management [56,57]. The only study included in this review to give a late assessment of PPI-related side-effects provides no information on minor side-effects at a distance from the initiation of treatment, even though these may have an impact on the patient's quality of life.

Long term PPI therapy is indicated for some patient populations [58] but should only be used when warranted and after consideration of potential adverse effects from long term use and ensuring benefits outweigh risks. Indeed, long-term PPI use is linked to serious systemic adverse effects such as *Clostridium difficile* infection, osteoporosis-related fractures, malabsorption of minerals (calcium, iron) and vitamins (B12.), dementia, kidney disease, respiratory disease, gastrointestinal infection, cardio-vascular disease and stroke [59–65]. Long-term PPI use may also have local adverse effects such as atrophic gastritis resulting from prolonged acid suppression, development of gastric polyps, chronic Helicobacter pylori infection and hypergastrinemia [66,67]. Hypergastrinemia can lead to an increased risk of gastric cancer [1].

Physicians who prescribe PPIs without any real indication contribute to the inappropriate use [68] leading to unnecessary continuation of therapy, exposing individuals to these adverse effects [23,69,70]. Lack of follow-up evaluation after ED discharge can also enhance the chronic consumption [35]. Therefore, according to published guidelines [5], it is important to de-prescribe PPIs to reduce the risk of adverse events [7]. In addition, in some countries these drugs are sold over the counter which can increase PPI misuse [71].

4.2. Limitations

This scoping review has several limitations even if it was conducted following the PRISMA-ScR process. First, the 3-database search strategy attempted to obtain an accurate overview, but may not have identified all available sources, especially those in the grey literature that were not used in the data search. Second, in the electronic database search strategy, only the names of 6 PPIs ("omeprazole" OR "pantoprazole" OR

"esomeprazole" OR "lansoprazole" OR "rabeprazole" OR "dexlansoprazole") corresponding to FDA-approved PPIs were used. Third, due to inclusion criteria, only articles in English were included. Fourth, only one study dealing with immediate safety and serious adverse events could be included in the review, and its inclusion population is not fully defined and probably correspond to larger inclusion criteria.

5. Conclusions

In primary care or emergency medicine, PPIs may have an analgesic action in acute pain conditions such as epigastric and non-chest thoracic pain of upper digestive tract origins with no or minor short-term side effects. No robust study allows recommendations about their use as a pain killer as first line or instead of classical analgesics in the ED. Data regarding the appropriateness of PPI testing are enough clear, even though they are used recurrently in primary care, particularly in a population with a high prevalence of GERD. Thus, it may be worthwhile to separate PPI use for diagnosed erosive digestive disease from PPI use for pain suspected to be due to an upper gastrointestinal tract disorder. Poor care practices with "one-size-fits-all" treatment for first management of upper gastrointestinal disorders, enhanced by lack of robust noninvasive tests, must be challenged. In addition, studies evaluating the impact of PPI test on the patient's care pathway are needed.

CRediT authorship contribution statement

Florence Carrouel: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Mikhail Dziadzko:** Writing – original draft, Writing – review & editing. **Charles Grégoire:** Writing – review & editing. **Michel Galinski:** Writing – review & editing. **Claude Dussart:** Writing – review & editing, Supervision. **Virginie-Eve Lvovschi:** Conceptualization, Investigation, Data curation, Writing – original draft. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The 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.

Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115523.

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