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USE OF PROTON PUMP INHIBITORS WITHOUT CLEAR INDICATION IN HOSPITALISED PATIENTS

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1. INTRODUCTION

Few drug classes have moved from specialist use to routine background therapy as quickly as the proton pump inhibitors (PPIs). Since omeprazole became available in the late 1980s, the class has become the standard treatment for acid-related disease, and its efficacy in healing ulcers and oesophagitis is not in doubt [1, 2]. The same reliability has made it easy to prescribe. A patient admitted with chest pain, a fracture or a chest infection often leaves with a PPI that nobody remembers starting. Commentators began

Abstract

Proton pump inhibitors are among the most widely prescribed medicines in hospitals, and a large share of that use has no documented indication. This review, which reports no new data, draws together published audits, trials, cohort studies and guidelines on the extent and causes of unindicated inpatient acid suppression. It covers the approved indications, the recurring patterns of overuse such as stress ulcer prophylaxis outside intensive care and unreviewed continuation at discharge, the associated harms and costs, and the stewardship measures that have been tried. Overuse is consistent across countries and specialities, whereas the harms attributed to long-term use rest largely on observational data. Few interventions have been tested with durable outcomes, and that gap limits firm practice recommendations.

warning about this drift more than fifteen years ago, describing a pattern of habitual

prescribing detached from any clear diagnosis [3, 4].

Hospital wards are where much of that drift begins. Surveys carried out in the United States, Italy, Australia and elsewhere have found that a substantial proportion of inpatients receiving acid suppression had no recorded reason for it [5, 6, 7, 8]. Prescribers often start the drug on admission as a precaution, continue it because it appeared on a previous list, or add it alongside anti-inflammatory or antithrombotic agents without weighing the actual bleeding risk. This review, which reports no new data, summarises what published studies show about unindicated PPI use in hospitalised adults, why it persists, what it costs, and which responses have been evaluated. The main findings are brought together in table 1.

Table 1: Selected published findings on PPI use without clear indication in hospitalised patients

Study or source setting	Principal finding	Ref.
Nardino et al. US hospital audit	Large share of inpatient acid-suppressive courses lacked an accepted indication	[5]
Parente et al. Italian hospitals	Hospital prescribing was frequently unjustified and shaped later community use	[6]
Pham et al. Medicine service	Routine prophylaxis in low-risk patients was the commonest unsupported reason	[7]
Cook et al. Intensive care cohort	Ventilation beyond 48 hours and coagulopathy predicted clinically important bleeding	[9]
Heidelbaugh and Inadomi Non-ICU wards	Unnecessary stress ulcer prophylaxis was common and often continued at discharge	[10]
Krag et al. SUP-ICU trial	Pantoprazole gave a small bleeding benefit without a difference in 90-day mortality	[11]
Herzig et al. Hospital cohort	Acid suppression was associated with hospital-acquired pneumonia	[12]
Janarthanan et al. Meta-analysis	PPI therapy was associated with <i>Clostridium difficile</i> infection	[13]
Yang et al. Case-control study	Long-term high-dose use was linked to hip fracture	[14]

Study or source setting	Principal finding	Ref.
Ahrens et al. Hospital to primary care	Discharge PPI recommendations often lacked an indication and were continued	[15]
Farrell et al. Guideline	Stepwise dose reduction or stopping is advised for resolved mild symptoms	[16]

2. PHARMACOLOGY AND ACCEPTED INDICATIONS

PPIs are substituted benzimidazole prodrugs that accumulate in the acidic canaliculi of parietal cells, where they convert to a reactive sulfenamide and bind covalently to the $H^+/K^+-ATPase$. Because the bond is irreversible, acid secretion recovers only as new pumps are synthesised, which explains why once-daily dosing gives prolonged suppression despite a plasma half-life of an hour or so [2]. Only pumps that are actively secreting are inhibited, so the effect builds over several days and is best achieved when the dose precedes a meal. These properties make the class potent and slow to wear off, which is useful for ulcer healing and less obviously useful for a patient with mild, intermittent dyspepsia.

Established indications are narrower than everyday practice suggests. They include healing and maintenance therapy in erosive oesophagitis, symptomatic gastro-oesophageal reflux disease responding to treatment, peptic ulcer disease, *Helicobacter pylori* eradication regimens, pathological hypersecretory states such as Zollinger-Ellison syndrome, and gastroprotection in patients at high risk of gastrointestinal bleeding from non-steroidal anti-inflammatory drugs or dual antiplatelet therapy [1, 17, 18]. After endoscopic treatment of a bleeding ulcer, high-dose intravenous or oral PPI therapy reduces rebleeding, and guidelines recommend it for a defined period [19]. Outside those situations, the evidence for benefit thins out quickly, and indications such as vague abdominal discomfort or generic gastric protection are poorly supported.

Dose and duration matter as much as the decision to start. A standard once-daily dose is adequate for most uncomplicated reflux

disease, yet audits of inpatient charts regularly find twice-daily or intravenous dosing where oral therapy would do, usually without a reason written down [7, 8]. Intravenous administration is justified when the patient cannot swallow or has active bleeding, but it is also more expensive and carries cannula-related risks. Review dates are rarely recorded. Without a stop date, a short-term hospital decision quietly turns into long-term therapy, which is where most of the avoidable exposure accumulates [15, 16].

Interactions are a second reason to ask whether a PPI is needed at all. Omeprazole and esomeprazole inhibit CYP2C19, the enzyme that activates clopidogrel, and pharmacodynamic studies showed reduced platelet inhibition when the two were combined, although the clinical meaning of that finding has been argued over ever since [1, 18]. Raised gastric pH also alters the absorption of drugs that need an acid medium, including some antifungals, iron salts and certain antiretrovirals. None of this makes a necessary PPI unsafe. It does mean that an unnecessary one adds a layer of pharmacokinetic complexity to a patient already taking many drugs, and ward pharmacists are well placed to notice when it does.

3. PATTERNS OF UNINDICATED USE IN HOSPITAL

One of the earliest systematic descriptions came from a teaching hospital audit in the United States, which found that most acid-suppressive prescriptions on general wards lacked an accepted indication, and that many of them were continued without reassessment [5]. Later studies from Italy, Australia and the United Kingdom reached similar conclusions in different health systems [4, 6, 20]. A study of an internal medicine service examined which diagnoses actually justified the drug and reported that routine prophylaxis in low-risk patients was the commonest unsupported reason [7]. The figures vary, but unindicated use accounted for somewhere between a third and well over half of inpatient courses in these reports.

Several recurring scenarios stand out. The first is stress ulcer prophylaxis in patients

outside intensive care, discussed in the next section. The second is the so-called gastroprotective PPI given with low-dose aspirin or a short NSAID course in a younger patient with no other bleeding risk factor. The third is continuation of a drug that was started for an acute problem, such as a bleed or a critical illness, long after the problem has resolved [8, 10]. A fourth, less discussed, is symptom-driven prescribing, in which any report of epigastric discomfort leads to a PPI instead of a review of the cause, whether that is food, alcohol, an irritant drug or anxiety [3, 21].

Admission medication reconciliation is the point at which many inpatient prescriptions are born. If the community list includes a PPI, the hospital chart usually does too, whether or not anyone can say why it was started. Studies of long-term outpatient use suggest that a considerable proportion of patients taking a PPI at home have no clear current indication either [21, 22]. The hospital therefore does not create the problem alone, but it is the place where a prescriber with the full record in front of them, and often a pharmacist beside them, has the best chance to ask the question [8, 15]. Too often the chart simply carries the drug forward.

The transition from hospital to community deserves its own attention. A German study following patients after discharge found that PPI recommendations in discharge letters were often not supported by a documented indication, and that general practitioners then continued them for long periods [15]. A Danish nationwide drug utilisation analysis showed how prevalent long-term adult use had become by the middle of the last decade, with a large fraction of users staying on treatment beyond a year [22]. Hospital initiation therefore has downstream consequences: an unreviewed inpatient prescription can become a decade of exposure. Parente and colleagues made the same point when they linked inpatient prescribing to what happened afterwards in general practice [6].

Differences between wards also appear in the audits. Surgical and orthopaedic patients are given acid suppression as part of routine peri-operative order sets, and elderly care

wards often have the highest burden of chronic use inherited from the community [7, 20]. Haematology and oncology patients, who may be on corticosteroids, anticoagulants or chemotherapy, are a genuinely higher-risk group for upper gastrointestinal complications, so some of the prescribing there is defensible. Reviewers have had to judge such cases individually, which is a reminder that blanket targets for reduction would be crude [8, 10]. The better question for any ward is whether each order has a stated reason that would survive a second reader.

4. STRESS ULCER PROPHYLAXIS

Stress ulcer prophylaxis is the best-defined setting in which PPIs are used without a sound indication. The foundation is a cohort study of critically ill patients in which respiratory failure needing mechanical ventilation for more than 48 hours and coagulopathy were the two independent predictors of clinically important bleeding [9]. Patients without those features had a very low bleeding risk. Prophylaxis was therefore built around a restricted group of patients in intensive care, and guidance has repeated that restriction. Yet hospital audits keep finding the drug prescribed to ward patients who have none of these risk factors, many of whom are simply old, unwell or on several medicines [8, 10].

A study estimating the size and cost of inappropriate prophylaxis in non-intensive hospitalised patients found that a considerable number were given acid suppression without a risk factor, and that a large share went home still taking it [10]. The most informative recent trial is the SUP-ICU study, a large blinded comparison of intravenous pantoprazole with placebo in ventilated or otherwise high-risk intensive care patients. Pantoprazole reduced clinically important gastrointestinal bleeding in a small way but made no difference to 90-day mortality [11]. If prophylaxis offers a modest effect even in the highest-risk units, the case for giving it to a ward patient at low risk is hard to sustain.

The harm side of stress ulcer prophylaxis is debated. Cohort data linked acid suppression with hospital-acquired pneumonia, with the

association appearing in patients on both histamine-2 antagonists and PPIs and roughly dose-related in some analyses [12]. Observational studies in hospital inpatients also reported an increase in *Clostridium difficile* infection among those prescribed PPIs [13, 23]. Confounding by indication is a real concern, since sicker patients receive more drugs, but the consistency of the signal across studies led several guideline groups to advise that prophylaxis be stopped as soon as the risk has passed and not carried onward to discharge [18, 24].

A practical reading of this evidence is fairly simple. Prophylaxis is reasonable in intensive care patients with defined risk factors, and it should have a documented stop point tied to extubation, resolution of coagulopathy or the start of enteral feeding. For ward patients, there is no good evidence of benefit from routine use. Table 1 sets these positions beside the findings on prevalence and harm so that readers can compare studies by design and setting, and the spread of entries by evidence theme is shown in fig. 1. Where a ward patient is judged to have an unusual bleeding risk, the reason should be written in the notes in a form that the next prescriber can read and challenge.

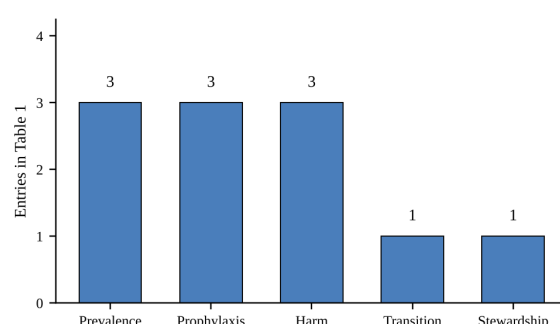


Fig. 1: Number of entries in table 1 by evidence theme

5. HARMS AND COSTS OF UNNECESSARY THERAPY

The case for restraint rests partly on adverse effects, although the strength of the evidence differs a great deal from one outcome to another. Hip fracture was among the first associations described, with higher risk in people taking high doses for more than a year in a large case-control study [14]. Later work linked long-term use with chronic kidney disease, hypomagnesaemia, vitamin B₁₂

deficiency and enteric infection [25, 26, 27]. Almost all of these findings come from observational cohorts in which residual confounding is hard to exclude, and the absolute risks, where they can be estimated, are small. Reviews have taken care to say so, even while recommending that long-term therapy be justified [18, 28, 29, 30].

Polypharmacy provides a further argument that is easy to overlook. Every extra drug adds a chance of interaction, an administration error or a pill that a patient cannot manage after discharge. Hypomagnesaemia, for instance, is more likely to matter in a patient who is also taking a loop or thiazide diuretic and may be at risk of arrhythmia, and the report that linked PPIs with low magnesium in a meta-analysis of observational studies suggests the effect is real though uncommon [26]. Reviews of adverse effects therefore frame the issue as one of cumulative burden, in which the PPI is one element of a long list that deserves periodic trimming [27, 28, 29].

Costs are easier to quantify than harms. Studies from the United States estimated the economic effect of inappropriate use of acid suppression in the ambulatory and inpatient settings, with spending in the hundreds of millions of dollars annually attributable to unindicated therapy [10, 31]. Intravenous PPI products are many times more expensive than oral generics, and their use in patients who could swallow tablets multiplies waste. Direct drug costs, though, are only part of the picture. Added doses require nursing time, intravenous access and pharmacy preparation, while follow-on events such as infection carry costs of their own that these analyses rarely capture [13, 31].

Older adults deserve particular mention because they receive the most PPIs, carry the heaviest medicine burden and are most exposed to the downstream risks of fracture, infection and falls. A benefit-risk review in this group concluded that the drug is valuable when a clear indication exists, and that evidence for continuing it without one is weak [32]. Deprescribing in the frail elderly is complicated by symptom rebound, which can follow withdrawal after prolonged use and is sometimes mistaken for relapse. That

rebound is usually temporary. Knowing about it in advance lets the prescriber and patient plan for it rather than abandon the attempt [16, 24].

6. STEWARDSHIP AND DEPRESCRIBING

Published interventions fall into a few categories. Guideline-based criteria embedded in order sets, pharmacist-led review of acid suppressants during ward rounds, automatic stop dates, restriction of intravenous formulations, and structured discharge reconciliation have all been described, usually in single-centre before-and-after studies [7, 8, 15]. Most reported reductions in inappropriate prescribing during the intervention period. Fewer followed patients long enough to tell whether the effect persisted, and almost none measured clinical outcomes. The weakness is not that the interventions fail, it is that the evidence for them is thin and short-lived, so each hospital tends to rebuild its own approach from first principles.

For patients already on long-term therapy, two guidelines give a usable framework. A Canadian evidence-based guideline recommends that patients treated for heartburn or mild reflux for four weeks with resolved symptoms should have the dose reduced or stopped, while those with severe oesophagitis, Barrett oesophagus or documented bleeding ulcers should continue [16]. An American Gastroenterological Association expert review reached comparable conclusions and added practical advice on tapering, on-demand use and monitoring [24]. Both emphasise shared decision-making, and both acknowledge that most of the supporting data come from trials of limited size and duration.

Measurement shapes what hospitals can learn. The simplest metric is the proportion of PPI orders with a documented indication on a given day, which a pharmacist can collect in an afternoon from the chart. More informative are the proportion with a stop or review date, the share of intravenous orders in patients taking other oral medicines, and the number of patients leaving with a PPI that was not on their admission list [7, 8, 33]. Repeating the

same audit after an intervention gives a local answer that published studies cannot, and makes it easier to see whether changes are holding or slowly sliding back into habit.

Admission is, in some respects, a favourable time to intervene. Medicines are reviewed, medication histories are rechecked, and patients and families expect changes to their regimens. A clinical pharmacist who examines each PPI order against explicit criteria can resolve most cases in a few minutes. Triggers worth building into review include any PPI without a recorded indication, any intravenous order in a patient taking other oral medicines, duration longer than the original plan, and prescriptions in patients without risk factors for bleeding [3, 8, 33]. These are simple, auditable standards, and they correspond to the failures that surveys most often identify.

Care is needed not to overcorrect. Patients with a history of bleeding ulcers who need aspirin, those on dual antiplatelet therapy with other risk factors, and people with severe erosive oesophagitis or Barrett oesophagus benefit from continued PPI therapy, and withdrawing it can cause harm [17, 18, 19]. Stewardship programmes that count every PPI as a target risk punishing appropriate prescribers and making clinicians suspicious of the whole exercise. The aim is accuracy, not minimisation. A defensible programme measures whether the right patients are receiving the drug for the right reason and for the right length of time, and not simply how many tablets were dispensed.

7. LIMITATIONS AND FUTURE DIRECTIONS

The literature on unindicated PPI use has limits that apply to this review too. Most audits are single-centre and cross-sectional, use different definitions of appropriateness, and come from a small number of countries. Reported prevalence therefore cannot be pooled in any simple way [21, 33]. Interventional studies are mostly uncontrolled, short and focused on process measures. The harm literature is observational, and the relation between dose, duration and outcome is unclear. Because this is a narrative review, selection of sources

reflects judgement as well as the available evidence, and readers should consult the cited guidelines for decisions about individual patients [18, 24].

Regional gaps deserve a mention. Much of the published audit work comes from North America, Western Europe and Australia, while data from low- and middle-income settings, where hospital pharmacy resources and formulary pressures differ, are comparatively few. It would be unwise to assume that the same patterns, or the same remedies, apply everywhere. Studies describing the economic effect have likewise been concentrated on a small number of health systems and on drug acquisition costs [10, 31]. Broader costing, including staff time and downstream events, would give hospital managers a clearer picture of what is at stake and help to justify the pharmacist time that stewardship requires.

Several questions remain open. Pragmatic trials of stewardship bundles with clinical outcomes, such as readmission, infection and bleeding, would give the strongest answer to whether reducing unindicated use matters to patients. Better electronic prompts, tested against simple alternatives like automatic stop dates, could show which components of a bundle do the work. Qualitative studies of prescribers, patients and pharmacists would help explain why habit survives knowledge. Finally, the effect of withdrawal on symptoms deserves larger controlled studies, so that deprescribing advice stands on firmer ground than expert opinion [16, 24, 27].

8. CONCLUSION

Proton pump inhibitors are effective drugs with a defined set of indications, and the published evidence shows consistently that a large part of their use in hospitalised patients falls outside those indications. The commonest patterns are stress ulcer prophylaxis in low-risk ward patients, precautionary gastroprotection, unreviewed continuation of acute-phase therapy and discharge prescriptions without a stated purpose (fig. 1) [5, 6, 10, 15]. The resulting waste is measurable, and the harms are small but plausible, particularly in older people on many medicines [14, 25, 32]. Where a

prescriber can name the indication, the dose and the planned end date, the drug is doing its job; where none of these can be named, the order deserves a second look.

Responses should be proportionate to the evidence. Documented indications, stop dates, restricted intravenous use and clear discharge information are low-cost measures that follow directly from the audits [7, 8, 16]. Deprescribing guidance exists and can be adapted for local use [18, 24]. What is lacking are well-controlled studies showing that these measures improve patient outcomes and hold up over time. Until such data appear, pharmacists and physicians can reasonably treat every PPI order as a decision with a purpose and an end date, and not as a default part of the admission routine [3, 31, 33].

9. ABBREVIATIONS

PPI-Proton pump inhibitor, NSAID-Non-steroidal anti-inflammatory drug, ICU-Intensive care unit, GERD-Gastro-oesophageal reflux disease, SUP-Stress ulcer prophylaxis, AGA-American Gastroenterological Association, CDI-Clostridium difficile infection, CKD-Chronic kidney disease

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. *Gut Liver* 2017;11:27–37.
2. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep* 2008;10:528–34.
3. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;336:2–3.
4. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. *J Clin Pharm Ther* 2000;25:333–40.
5. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol* 2000;95:3118–22.
6. Parente F, Cucino C, Gallus S, Bargiggia S, Greco S, Pastore L, *et al.* Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment Pharmacol Ther* 2003;17:1503–6.
7. Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother* 2006;40:1261–6.
8. Reid M, Keniston A, Heller JC, Miller M, Medvedev S, Albert RK. Inappropriate prescribing of proton pump inhibitors in hospitalized patients. *J Hosp Med* 2012;7:421–5.
9. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Wang Q, Rutledge F, *et al.* Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994;330:377–81.
10. Heidelbaugh JJ, Inadomi JM. Magnitude and economic impact of inappropriate use of stress ulcer prophylaxis in non-ICU hospitalized patients. *Am J Gastroenterol* 2006;101:2200–5.
11. Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, *et al.* Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018;379:2199–208.
12. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009;301:2120–8.
13. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012;107:1001–10.
14. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947–53.
15. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot JF. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. *Int J Clin Pract* 2012;66:767–73.
16. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, *et al.* Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354–64.
17. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J*

- Gastroenterol 2013;108:308–28.
18. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology* 2017;152:706–15.
19. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107:345–60.
20. Gupta R, Garg P, Kottoor R, Munoz JC, Jamal MM, Lambiase LR, *et al.* Overuse of acid suppression therapy in hospitalized patients. *South Med J* 2010;103:207–11.
21. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012;5:219–32.
22. Pottegård A, Broe A, Hallas J, de Muckadell OB, Lassen AT, Lødrup AB. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. *Therap Adv Gastroenterol* 2016;9:671–8.
23. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ* 2004;171:33–8.
24. Targownik LE, Fisher DA, Saini SD. AGA clinical practice update on de-prescribing of proton pump inhibitors: expert review. *Gastroenterology* 2022;162:1334–42.
25. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, *et al.* Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016;176:238–46.
26. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ratanapo S, *et al.* Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. *Ren Fail* 2015;37:1237–41.
27. Haastrup PF, Thompson W, Søndergaard J, Jarbøl DE. Side effects of long-term proton pump inhibitor use: a review. *Basic Clin Pharmacol Toxicol* 2018;123:114–21.
28. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. *JAMA Intern Med* 2016;176:172–4.
29. Eusebi LH, Rabitti S, Artesiani ML, Gelli D, Montagnani M, Zagari RM, *et al.* Proton pump inhibitors: risks of long-term use. *J Gastroenterol Hepatol* 2017;32:1295–302.
30. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases: a position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016;14:179.
31. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care* 2010;16:e228–34.
32. Masclee GM, Sturkenboom MC, Kuipers EJ. A benefit-risk assessment of the use of proton pump inhibitors in elderly patients. *Drugs Aging* 2014;31:263–82.
33. Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal. *Eur J Intern Med* 2017;37:19–24.