

Original Research

Analysis and improvement measures of rational use of proton pump inhibitors for injection by clinical pharmacists

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Abstract

Objective: To analyze the irrational use of proton pump inhibitors for injection in clinic and its causes, and to promote the standardized use of proton pump inhibitors in hospital by clinical pharmacists by taking corresponding intervention measures. **Methods:** The use of proton pump inhibitors from January to March 2024 was collected through the rational drug use system of The Second Affiliated Hospital of Xuzhou Medical University, and the problems of irrational drug use during the use of proton pump inhibitors were classified, statistically summarized. **Results:** From January to March 2024, a total of 2363 inpatients in The Second Affiliated Hospital of Xuzhou Medical University were prescribed proton pump inhibitors for injection, including 1321 orders for esomeprazole for injection, 804 orders for omeprazole for injection, 166 orders for ipirazole for injection, 64 orders for Pantoprazole for injection, and 8 orders for rhapsazole for injection. There were 55 cases of unreasonable medical orders for drug use, and the irrational types of clinical drug use mainly included 24 unsuitable indications (43.64% of unreasonable medical orders). The selected drugs were not suitable in 7 cases (unreasonable medical advice accounted for 12.73%); Inappropriate usage and dosage in 19 cases (34.55%); There were 3 cases (5.45%) of unreasonable combination and 2 cases (3.64%) of unreasonable repeated administration. **Conclusion:** There are many unreasonable situations in the use of proton pump inhibitors for injection in our hospital. Clinical pharmacists will be committed to promoting hospitals to introduce a number of initiatives to standardize the use of proton pump inhibitors and improve the level of rational use of proton pump inhibitors.

Keywords: Proton pump inhibitors for injection; Clinical pharmacist; Rational drug use; Omeprazole; Esomeprazole

INTRODUCTION

Proton pump inhibitors (PPIs) are currently the most effective acid secretion inhibitors in a commonly used class of drugs used to treat gastroesophageal reflux disease and other conditions with excess stomach acid. Common clinical injections of this class of drugs include omeprazole, esomeprazole, pantoprazole and ilaprazole. In recent years, there have been irrational use of proton pump inhibitors in clinical application, including drug use without indication, inappropriate selection of drugs, inappropriate usage and dosage, and inappropriate combination of drugs, etc., which may increase the risk and economic burden of medication for patients¹⁻³. As the society increasingly attaches importance to standardized and rational drug use⁴, in this paper, statistics and summary of the drug use of proton pump inhibitors from January to March 2024 were made to analyze the causes of clinical irrational drug use, reduce the incidence of adverse drug reactions, and improve the rationality of drug use⁵.

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METHODS

Data source

The details of inpatients with PPI injections from January to March 2024 were extracted through the Ruimei Rational Drug Use system and information management system of The Second Affiliated Hospital of Xuzhou Medical University, and according to the patients' disease diagnosis, disease degree, liver and kidney function, fasting and nasal feeding doctor's orders, etc. The rationality of PPI injection was analyzed and evaluated from the aspects of indication, drug selection, usage and dosage, combined use, etc.

Methods

According to proton pump inhibitor drug instructions, Guiding Principles for Clinical Application of Proton pump Inhibitors (2020)⁶, Expert Consensus on Optimal Application of proton pump Inhibitors (2020)⁷, Chinese Expert Consensus on Prevention and Treatment of Post-traumatic Stress Ulcer⁸, Expert Recommendations on Prevention and Treatment of Stress Ulcer (2018 edition)⁹, "Guidelines for Primary Diagnosis and Treatment of Gastroesophageal Reflux Disease (2019)"¹⁰, "Guidelines for the Treatment of Helicobacter Pylori Infection in China 2022"¹¹, "Expert Consensus on Prophylactic Use of proton pump Inhibitors (2018)"¹², "Expert Guidance on Prophylactic Use of Proton pump Inhibitors and Prescription Simplification (2019)"¹³, "Children Expert Consensus on Rational use of proton pump inhibitors in Children (2019 edition)"¹⁴, Consensus on Diagnosis and Treatment of Functional dyspepsia in Chinese Children (2022 edition)¹⁵, Expert Consensus on Prevention and Treatment of nausea and vomiting related to cancer drug



Therapy (2019 edition)¹⁶, and relevant literature in various databases. Discuss and formulate the key points of rational use of proton pump inhibitor injections (Table 1) and the evaluation criteria for rational use of proton pump inhibitors in clinical patients (Table 2), and conduct special comments and interventions on the suitability of drug use of proton pump inhibitors for injection in inpatients. The workflow of clinical pharmacist was illustrated in Figure 1.

RESULTS

Use of proton pump inhibitors Basic situation of the use of proton pump inhibitors in The Second Affiliated Hospital of Xuzhou Medical University from January to March 2024, with a total of 2363 medical orders. The number of medical orders for each PPI injection in clinical application and the number used are shown in Table 2. Gastroenterology, radiotherapy, and general surgery were the departments with a large number of medical orders for PPI injection reviews, and the distribution of the main departments used was shown in Table 3.

In this random check, there were 2363 medical orders for rational use of PPI injections (97.67%) and 55 unreasonable medical orders (2.33%). Inappropriateness of indications was the most serious problem found in this review, with 24 cases (unreasonable medical orders accounted for 43.64%); The selected drugs were not suitable in 7 cases (unreasonable

medical advice accounted for 12.73%); Inappropriate usage and dosage in 19 cases (34.55%); There were 3 cases (5.45%) of unreasonable combination and 2 cases (3.64%) of unreasonable repeated administration was shown in Table 4. The types of irrational use mainly include unsuitable indications, unsuitable drug selection, unsuitable usage and dosage, unreasonable combination of drug use, etc., as shown in Table 5.

DISCUSSION

Unreasonable use of PPI injection

Inappropriate indications:

In our hospital, PPI injections were mainly used for preventive use, with a total of 1332 medical orders (56.37%), which were mainly used for the prevention and treatment of vomiting related to tumor treatment, the prevention of postoperative stress ulcers of digestive tract mucosa and the prevention and treatment of drug-related stress ulcers. The commonly used departments mainly included radiotherapy, general surgery and oncology. Therapeutic use of 1031 medical orders (43.63%), mainly for reflux esophagitis, upper gastrointestinal bleeding, mainly in the department of gastroenterology, general medicine, etc. Among them, 24 cases were used without indication, mainly for upper gallstones, bronchitis, thyroid nodules and so on.

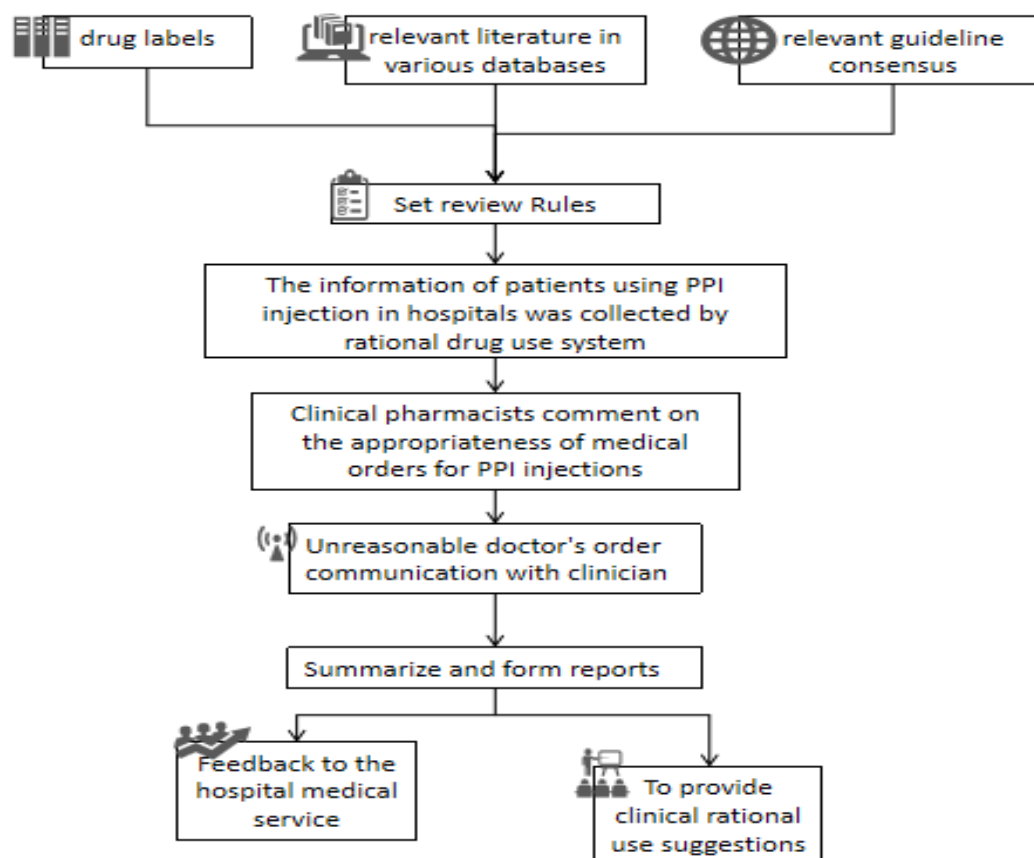


Figure 1. Flow chart of clinical pharmacist intervention.

Table 1: Key points of rational use of proton pump inhibitor injections.

Drug Name (Injection)	indication	Key points of rational drug use
Omeprazole	Peptic ulcer bleeding, anastomotic ulcer bleeding; The acute gastric mucosal injury and the acute gastric mucosal injury caused by non-steroidal anti-inflammatory drugs were observed during stress; Prevention of severe diseases (such as cerebral hemorrhage, severe trauma, etc.) stress state and upper gastrointestinal bleeding caused by gastric surgery; As an alternative treatment for the following conditions when oral therapy is not appropriate: duodenal ulcer, gastric ulcer, reflux esophagitis, and Zuo-Ai syndrome;	<ol style="list-style-type: none"> 1. Intravenous injection of 60mg is recommended as the starting dose for patients with Zuo-Ai syndrome, once a day. Twice when the daily dose exceeds 60mg; 2. Omeprazole sodium for injection (for intravenous injection only) should be injected 10 mL of special solvent into a freeze-dried powder vial before use, and other solvents should not be dissolved to prepare; 3. Omeprazole sodium for injection (for intravenous infusion only) powder injection should be dissolved in 100mL 0.9% sodium chloride injection or 100mL 5% glucose injection. Do not dissolve or dilute with other solvents or drugs; 4. Omeprazole sodium for injection (for intravenous injection only) must be used within 4 hours after dissolution. Omeprazole sodium for injection (for intravenous infusion only) should be used within 6 hours after being dissolved in 5% glucose injection; Soluble in 0.9% sodium chloride injection can be used within 12 hours;
Esomeprazole	As an alternative therapy for GERD when oral therapy is not available; For low-risk patients with bleeding from acute gastric or duodenal ulcers for which oral therapy is not appropriate (Forrest grade c-I11 under gastroscopy); To reduce the risk of rebleeding after endoscopic treatment for bleeding from gastric and duodenal ulcers in adults;	<ol style="list-style-type: none"> 1. For GERD patients who cannot take oral medication, short-term medication (no more than 7 days) should be used, and when possible, oral therapy should be switched to; 2. For patients with acute gastric or duodenal ulcer bleeding who cannot be orally administered Forrest grade IIc-III, intravenous injection of 40mg of this product is recommended every 12 hours for 5 days; 3. After endoscopic treatment of acute bleeding from gastric and duodenal ulcers, patients should be given 80mg esomeprazole intravenously for 30 minutes, followed by continuous intravenous infusion of 8 mg/h for 71.5 hours; 4. The injection is prepared by adding 5mL 0.9% sodium chloride injection into the vial for intravenous injection; 5. The infusion solution is prepared by dissolving into 100mL 0.9% sodium chloride injection for intravenous infusion;
Pantoprazole	Duodenal ulcer; Gastric ulcer; Moderate to severe reflux esophagitis; Acute upper gastrointestinal bleeding caused by duodenal ulcer, gastric ulcer, acute gastric mucosal lesion, complex gastric ulcer, etc;	<ol style="list-style-type: none"> 1. static push, static drop can be; 2. only short-term (no more than 7 to 10 days) for patients who should not be taken orally. Pantoprazole for injection should not be continued once the patient is able to take the drug orally; 3. Before clinical use, 10 mL 0.9% sodium chloride injection is injected into a freeze-dried powder vial, which can be directly injected intravenously for more than 2 minutes; The dissolved liquid can also be added to 100mL 0.9% sodium chloride injection or 5% glucose injection after dilution and intravenous drip, within 15 to 60 minutes;
Rabeprazole	For gastric and duodenal ulcer bleeding where oral therapy is not applicable;	<ol style="list-style-type: none"> 1. The injection is for intravenous infusion only, and the course of treatment does not exceed 5 days. Once patients can be given orally, they should be changed to oral formulations; 2. Dissolve 5 mL 0.9% sodium chloride injection before immediate use, add the dissolved solution into 100mL 0.9% sodium chloride injection, dilute it and provide intravenous infusion, which should be completed within 15 to 30 minutes;

Iprrazole	Gastrointestinal ulcer bleeding;	<p>1. The injection is for intravenous infusion only. The initial dose was 20mg, followed by 10mg once a day for 3 days. After the course of treatment, oral therapy can be changed according to the situation;</p> <p>2. The injection of 10 mg was completely dissolved in 100 mL 0.9% sodium chloride injection, and was administered intravenously through an infusion set with a filter device for 30 minutes. At the initial dose of 20 mg, 200 mL 0.9% sodium chloride injection was used to dissolve;</p>
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Table 2: Evaluation criteria for rational use of proton pump inhibitors in clinical patients

Name of index	Rational	Irrational
Indication	Suitable for indications;	Indications are not suitable;
Drug selection	The selected drugs are suitable;	The selected drug is not suitable (including those who do not prefer national essential medicines without justifiable reasons);
Usage and dosage	Appropriate usage and dosage;	Inappropriate usage and dosage. (including inappropriate drug dosage forms or routes of administration);
Drug combination	The combination of drugs is appropriate;	The combination of drugs is not appropriate. (including incompatibility or adverse interactions);
Repeated administration	No repeated administration;	Repeated administration;

Table 3: The number of medical orders of commonly used PPI injections in clinical practice and the quantity used.

Drug names(injection)	Number of doctor's orders	The number of injections (bottles)
sOmeprazole	804	2108
Esomeprazole	1321	2913
Pantoprazole	64	104
Rabeprazole	8	15
Iprrazole	166	219

Table 4: Lists the number of medical orders for the use of PPI injections in the top 14 wards

Inpatient ward	Esomeprazole	Omeprazole	Pantoprazole	Rabeprazole	Iprrazole
Gastroenterology dept.	494	256	6	0	14
Radiation oncology dept.	327	198	0	0	26
Department of general surgery	97	85	4	2	11
MBBS	82	66	0	0	12
Orthopedics dept.	77	88	0	0	3
RICU	75	54	0	0	10
Invasive Technology dept.	60	36	2	0	0
Urology surgery dept.	46	14	0	0	2
Rehabilitation dept.	39	22	0	0	0
Medical oncology dept.	24	12	0	3	0
Neurology dept.	21	8	0	0	0
Cardiology dept.	17	10	0	0	0
Nephrology dept.	17	19	0	0	0
ICU	10	14	0	0	0
Sum	1386	882	12	5	78



Table 5: Unreasonable types and unreasonable use of PPI injections (orders)						
Unreasonable type	Esomeprazole	Omeprazole	Pantoprazole	Rabeprazole	Iprazole	Summarization
The indication is not suitable	13	8	1	1	1	24
Drug selection is not appropriate	4	3	0	0	0	7
Usage and dosage are not appropriate	9	8	1	0	1	19
Combination medication is not appropriate	2	1	0	0	0	3
Repeated administration	1	1	0	0	0	2

Indications of no preventive medication: Stress ulcer is the most common and serious complication in critically ill patients. Stress ulcer causes gastrointestinal bleeding, perforation, and mortality of 50%-80%. Special attention should be paid to prevention. However, according to the Guiding Principles, the operation time of general surgery and orthopaedic surgery is usually less than 3h, which is rarely a major complex operation, and the risk of stress mucosal lesions is low. Most patients only need to fast briefly after surgery, and routine preventive use of PPI injection preparations is not recommended¹⁷. The review found that it was unreasonable to use PPIs to prevent stress ulcers in patients undergoing laparoscopic surgery in general surgery and orthopaedic surgery in our hospital. The patient in the respiratory department was diagnosed with "chronic bronchitis" and had symptoms of chest tightness and discomfort. Prophylactic use of PPIs showed no indication of medication. For oncology chemotherapy patients, the NCCN Guidelines for Antiemesis (version 2023.v2)¹⁸ and the Guidelines for Drug Prevention and Treatment of chemotherapy-induced nausea and Vomiting (2022)¹⁹ do not recommend prophylactic use of PPIs before conventional chemotherapy, but the use of PPIs during chemotherapy can be considered to improve patients' acid reflux and nausea symptoms²⁰. The review found that some chemotherapy patients did not evaluate the basic situation of patients during chemotherapy, and directly used PPI injections, which belonged to unclear drug indications.

Indications of non-therapeutic drug use: According to Expert Consensus on Prophylactic Application of proton pump Inhibitors (2018)¹², patients diagnosed with "gallstones" in the department of gastroenterology were routinely given PPIs; General surgery patients with clinical diagnosis of "acute appendicitis", "thyroid nodules" and "allergic dermatitis" were routinely given PPIs; Patients with clinical diagnosis of vertigo in the department of neurology were given omeprazole 40mg, twice a day, and the above patients were generally OK during hospitalization, without symptoms of digestive tract discomfort, and were given without indications. In addition, there are also cases where the doctor's order is inconsistent with the description of the course record, such as the doctor's order to fast, the course of the disease can write food, but it is still unreasonable to give PPIs.

Inappropriate selection of drugs:

Currently commonly used PPIs mainly includes omeprazole, esomeprazole, Pantoprazole, Rabeprazole and iprrazole. According to the New Understanding of Proton Pump

Inhibitors Related Kidney Injury²¹ and the drug instructions, esomeprazole should not be used in patients with moderate or severe liver and kidney dysfunction. The review found that the use of esomeprazole injection in patients with severe renal insufficiency in the department of renal medicine was unreasonable, and it was recommended to replace the use of omeprazole injection. In addition, omeprazole for injection is suitable for alternative treatment of diseases such as duodenal ulcer, gastric ulcer and reflux esophagitis where oral therapy is not appropriate, and injections are not recommended when oral preparations can be used.

Inappropriate Usage and dosage:

Ultra-course of drug use mainly refers to the patient's days of drug use exceeding the drug course specified in the instructions. For patients with peptic ulcer bleeding, the course of treatment requires continuous drug use for 3d, and oral treatment can be changed according to the situation after the course of treatment. Elective surgery generally does not fasting or only fasting for a short period of time, generally ≤7 days, when the patient can gradually restore the diet and clinical condition is good, it can be replaced by oral administration. The "Guiding Principles" also clearly states that the patient's condition is improved, stable, can tolerate enteral nutrition or can eat when the stop. The review found that in the gastroenterology department of our hospital, PPIs were given to patients with gastric mucosal lesions after endoscopic submucosal dissection to prevent bleeding and promote the healing of artificial ulcers until discharge. From the day of surgery, esomeprazole was injected 40mg, once every 12 hours, and the administration time was too long for 14 days. The review also found that prophylactic use of therapeutic doses of PPIs, such as orthopedic surgery patients to prevent stress ulcer prophylactic use of omeprazole sodium injection, 40mg, twice a day, intravenous drip, the dose is too large is unreasonable. The use of PPI injections for patients with liver dysfunction in the infectious department and 12-year-old pediatric patients failed to adjust the dosage according to the liver function or age and weight of the child, and the review was unreasonable

Unreasonable combination of drug use:

During the review of PPI injection, it was found that the general surgery department clinically diagnosed "acute cholecystitis and cholelithiasis after operation" and simultaneously administered ranitidine 50mg once a day + omeprazole 40mg injection twice a day for acid inhibition and stomach protection.



PPIs inhibit the final process of gastric acid secretion in gastric parietal cells, resulting in a strong acid inhibition effect, while H₂ receptor blockers are less effective than PPIs, and the acid inhibition intensity of PPIs are weakened by the administration of these two drugs at the same time. If nocturnal acid breakthrough symptoms exist, H₂ receptor antagonists can be added before bed or at night, but PPIs are not recommended to be used with other acid suppressors. In addition, PPIs' inhibition of gastric acid secretion can significantly increase the pH value in the stomach of patients, resulting in decreased drug absorption of gastric acid dependence or solubility, and decreased blood drug concentration, which affects the clinical therapeutic effect. The review found that the clinical use of gastric mucosal protective agent sulfoaluminum suspension gel combined with PPIs, due to the strong dependence of sulfoaluminum on acidic environment, The simultaneous use of PPIs will prevent sucralosal from being fully acidified, resulting in poor efficacy. Clinically, omeprazole combined with clopidogrel may reduce the pharmacological effects of clopidogrel and lead to increased cardiovascular and cerebrovascular risk, which is mainly related to the competition between the two liver drug enzymes such as CYP2C19. The two are associated with the reduction of liver metabolism of clopidogrel, resulting in the reduction of the level of active metabolites of clopidogrel. Therefore, the platelet inhibitory aggregation efficiency of clopidogrel is reduced, so the combination of drugs is not suitable.

Repeated drug use:

The patient in the department of gastroenterology was clinically diagnosed as "vesicular gastritis", and the doctor advised to give PPIs oral dosage form and PPIs injection dosage form at the same time, which is repeated drug use and unreasonable.

Cause analysis and pharmaceutical intervention measures

Based on the review and analysis of the medical instructions for the clinical use of PPI injections in The Second Affiliated Hospital of Xuzhou Medical University from January to March 2024, the irrational use of PPI injections in our hospital mainly involved inappropriate indications, inappropriate selection of drugs, inappropriate usage and dosage, and the overall irrational rate was relatively high. The main reasons were as follows: (1) The functional departments of the hospital did not have enough special assessment and reward and punishment for the rational use of PPIs²²; (2) Doctors' improper grasp of the indications for the use of PPI injections; (3) The hospital rational drug use system and prescription review pharmacists have insufficient intervention on unreasonable prescription orders⁴; (4) Insufficient guidance and education of clinical pharmacists on clinical rational drug use; (5) Clinical drug use is also affected by other economic and ethical factors. Irrational use of PPIs can lead to increased incidence of adverse reactions, increased medication risk for patients, and increased medical expenses.

In response to the above problems, clinical pharmacists will take the following measures: (1) Clinical pharmacists will promote

the Pharmaceutical Administration Committee to include PPIs into the list of key monitored drugs in the hospital, and at the same time conduct control from the information system, so that more than two kinds of adjuvant drugs cannot be used at the same time within 24 hours, and implement supervision and assessment²³; (2) Promote the hospital to issue the "Notice on Further Regulating the Clinical Application of proton pump inhibitors", develop and improve the special rules for proton pump comments in clinical pharmacy, submit them to the expert working group for rational drug use for review, and form the specifications for proton pump special comments²⁴; (3) Implementation of the proton pump special assessment system: The original assessment according to the department was changed to the assessment according to the diagnosis and treatment team, so as to make the assessment more detailed. Clinical pharmacists were required to make special comments on proton pump inhibitors every month, and the results of the comments were summarized to the medical office, which then organized an expert review, reported the relevant doctors and departments with unreasonable drug use in the medical quality briefing, and included in the performance assessment of the departments. It is linked with doctors' evaluation, prescription right and promotion; (4) Maintain indications, combined medication and limited scope of use in the Mulao Rengang Medical intelligence and decision support system, maintain reminders and options for limited payment amount in HIS system, and pay at your own expense if you exceed the scope of use and payment amount; (5) Increase clinical publicity and training, clinical pharmacists do a good job of pharmaceutical care, patient education, regular training and assessment of clinical diagnosis and treatment team, continuous assessment fails, the use of unreasonable doctors will be reported to the medical office for prescription authority limits.

CONCLUSION

To sum up, there are obvious problems in the therapeutic and preventive use of PPI drugs in hospitals. Clinical pharmacists actively promote hospitals to introduce a number of measures to further regulate the use of PPIs, improve the rational use of proton pump inhibitors, and better serve patients.

AUTHORS' CONTRIBUTIONS

Conceptualization-writing and editing, Huanjie Li; review, Nannan Yin; data summary and visualization, Jiahui Ye . All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results



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