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Cardiovascular risk with long-term use of proton pump inhibitors

Trukhan D.I.

Federal State Budgetary Institution of Higher Education "Omsk State Medical University" of the Ministry of Health of the Russian Federation, Omsk, Russia.

AUTHOR

Dmitry I. Trukhan*, PhD, MD, Associate Professor, Professor of the Department of Polyclinic Therapy and Internal Diseases, Federal State Budgetary Educational Institution of Higher Education "Omsk State Medical University" of the Ministry of Health of the Russian Federation, Omsk, Russia. ORCID: 0000-0002-1597-1876

Proton pump inhibitors (PPIs) are the most effective drugs for the treatment of acid-dependent diseases. From gastroenterological practice, PPIs are being actively introduced into other specialties, particularly cardiology and rheumatology, where they are used to protect the gastrointestinal mucosa and prevent gastrointestinal bleeding during long-term antithrombotic therapy and long-term use of nonsteroidal anti-inflammatory drugs.

Objective of this review is to present and analyze data from international and national studies on the presence of cardiovascular risk with long-term PPI use.

Material and methods. The article uses materials from peer-reviewed articles published in PubMed, Scopus, and e-library.ru from 2013 to 2025 using the keywords: proton pump inhibitors, cardiovascular risk, myocardial infarction, arterial hypertension, stroke, arrhythmias, rhabdomyolysis.

Results. In the current decade, a number of international reviews have been published examining the associations between long-term PPI use and a range of diseases/conditions, including the cardiovascular risk associated with their use. The data presented in the review suggest a possible association between long-term PPI use and the development of myocardial infarction, arterial hypertension, stroke, and cardiac arrhythmias.

Conclusion. Increasing awareness among physicians and patients about the appropriate use of PPIs and knowledge of the adverse effects of long-term therapy will optimize the use of these drugs in real clinical practice, especially in comorbid patients with cardiovascular disease.

Keywords: proton pump inhibitors, cardiovascular risk, myocardial infarction, arterial hypertension, stroke, arrhythmias, rhabdomyolysis.

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* Corresponding author. Tel. +7 (381) 295-72-77. E-mail: dmitry_trukhan@mail.ru

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Introduction

Cardiovascular diseases (CVDs) occupy a leading place in the structure of chronic noncommunicable pathology in the adult population and are the main cause of premature death and early disability in most economically developed countries. In the Russian Federation, according to Rosstat, in 2023 the total number of deaths due to diseases of the circulatory system was 814.4 thousand people, which corresponds to 46% of all cases.

Proton pump inhibitors (PPIs) are considered the most effective drugs for the treatment of acidrelated diseases. In recent decades, the use of PPIs has grown exponentially [1]. From gastroenterological practice, PPIs are being actively introduced into other specialties, in particular cardiology and rheumatology, where they are used to protect the gastrointestinal mucosa and prevent gastrointestinal bleeding during longterm antithrombotic therapy and longterm use of nonsteroidal antiinflammatory drugs (NSAIDs).

Since the appearance of the first PPI, omeprazole, on the pharmaceutical market (1988), for a long period of time PPIs were considered safe drugs for shortterm and longterm use [2]. However, current clinical guidelines note that when prescribing PPIs in high doses for a long period, the possibility of adverse effects should be considered. In recent years, a number of international reviews have been published that examine the associations between PPIs and various diseases/conditions, including the possible association of PPI use with an increased risk of cardiovascular complications.

The aim of this review article is to present and analyze data from international and national studies on the possible presence of cardiovascular risk (CVR) with longterm use of PPIs.

Material and methods

In preparing this article, materials from peerreviewed articles published in PubMed, Scopus and e-library.ru from 2013 to 2025 were used, using the keywords: proton pump inhibitors, cardiovascular risk, myocardial infarction, arterial hypertension, stroke, cardiac arrhythmias, rhabdomyolysis.

Results

Proton pump inhibitors and overall cardiovascular risk

Increased CVR with longterm PPI use may be related to a number of factors: increased plasma levels of asymmetric dimethylarginine (ADMA), which reduces nitric oxide (NO) production in vessels by competitively inhibiting nitric oxide synthase (NOS) [3]; endothelial dysfunction, hypomagnesaemia and hypocalcaemia, decreased levels of vitamins C and B12 [4, 5]. Longterm PPI use may result in endothelial cell dysfunction, accelerated endothelial ageing, increased oxidative stress, hyperinflammation and premature vascular ageing [6]. Examples of this relationship are shown in several studies.

For example, in the US ARIC (Atherosclerosis Risk in Communities) study involving 4,436 participants, patients taking PPIs [7] more often had hypomagnesaemia (≤0.75 mmol/L) (hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.081.44); during a 5 year follow up, 684 cases of CVD occurred. PPI users had a higher risk of CVD (HR 1.31; 95% CI 1.10–1.57) than nonusers.

In a retrospective Thai cohort study of 3,928 patients taking PPIs and 3,928 patients taking H2antihistamines [8], an association was found between PPI use and CVD (HR 1.76; 95% CI 1.40–2.20), ischaemic stroke (IS) (HR 3.53; 95% CI 2.21–5.64) and peripheral vascular disease (HR 17.07; 95% CI 13.82–76.25) compared with H2antihistamine use. The association between PPIs and each outcome was significant with a medication possession ratio >50%. Furthermore, the association between PPIs and diseases of the circulatory system was robust to unmeasured confounders (e.g., smoking and alcohol).

A ChineseAmerican prospective cohort study [9] demonstrated an association between regular PPI use and cardiovascular outcomes (459,207 participants without CVD were identified). Over a follow-up of more than 8 years, the researchers recorded 26,346 cases of CVD (including 13,749 cases of coronary heart disease (CHD), 4,144 cases of stroke, 5,812 cases of atrial fibrillation (AF), 1,159 cases of heart failure (HF), and 4,206 cases of venous throm-

boembolism). Fully adjusted hazard ratios (AHRs) in PPI users were elevated compared with nonusers and were noted for all CVD events (AHR 1.44; 95% CI 1.39–1.50), for CHD (AHR 1.65; 95% CI 1.57–1.74), for stroke (AHR 1.21; 95% CI 1.09–1.33), for AF (AHR 1.17; 95% CI 1.08–1.28), for HF (AHR 1.61; 95% CI 1.37–1.89) and for venous thromboembolism (AHR 1.36; 95% CI 1.24–1.50). The researchers note that regular PPI use was associated with higher CV risk, and therefore caution is needed when prescribing PPIs.

In an Italian populationbased cohort study of 284,068 patients (49.4% PPI users, 50.6% nonusers) [10], the risk of CVD and death in elderly people with diabetes mellitus (DM) was studied. Over a median followup of 6.7 years, PPI use was associated with a higher risk of IS (HR 1.14; 95% CI 1.08–1.20), myocardial infarction (MI) (HR 1.36; 95% CI 1.31–1.41) and allcause mortality (HR 1.24; 95% CI 1.22–1.26). These risks were elevated regardless of the specific PPI agent used.

According to a metaanalysis (17 studies, 7,540 participants) conducted by Chinese pharmacologists and gastroenterologists [11], patients taking PPIs had a 70% higher risk of major cardiovascular events (HR 1.70; 95% CI 1.132.56; p=0.01). The highest risk of adverse cardiovascular events was noted in the subgroup of longterm PPI use (HR 2.33; 95% CI 1.334.08; p=0.003) and in those taking omeprazole (HR 3.17; 95% CI 1.437.03; p=0.004).

In a metaanalysis of 11 studies by Chinese cardiologists [12], clopidogrel monotherapy (55,494 patients) was compared with clopidogrel + PPI therapy (29,235 patients). Patients taking PPIs had an increased risk of major adverse cardiovascular events (odds ratio (OR) 1.37; 95% CI: 1.23–1.53; p <0.00001), MI (OR 1.41; 95% CI: 1.26–1.57; p <0.00001), target vessel revascularization (OR 1.28; 95% CI: 1.011.61; p = 0.04) and stent thrombosis (OR 1.38; 95% CI: 1.13–1.70; p = 0.002). In another metaanalysis of 15 studies involving 50,366 patients, Chinese cardiologists demonstrated [13] that patients not taking PPIs had a significantly reduced risk of major adverse cardiovascular events (MACE) (HR 0.82; 95% CI 0.770.88), stroke (HR 0.72; 95% CI 0.670.76), recurrent MI (HR 0.72; 95% CI 0.570.90), target vessel revascularization (HR 0.77; 95% CI 0.630.93) and stent thrombosis (HR 0.71; 95% CI 0.560.92).

American scientists studied 85,189 postmenopausal women (mean age 63 years at baseline) without known CVD at enrolment in the observational Women's Health Initiative study [14]. At baseline, 1,747 (2.1%) women reported PPI use. Over a mean followup of 11 years, 5,778 (6.8%) cases of primary CVD were identified. In patients taking PPIs, the risk of developing CVD was significantly higher than in those not taking them (HR 1.21; 95% CI: 1.02–1.43). Longer PPI use was associated with a gradually increasing risk of CVD (HR <1 year: 1.11; 1–3 years: 1.27; >3 years: 1.33; p = 0.02).

Proton pump inhibitors and myocardial infarction

The increased risk of MI may be related to elevated ADMA levels, which block the enzyme dimethylarginine dimethylaminohydrolase (DDAH). NOS is blocked by ADMA, leading to decreased NO production, enhanced vasoconstriction and reduced vasodilation [15].

In a Taiwanese cohort study of 27,624 patients using PPIs who subsequently developed acute MI (AMI) and 27,624 control subjects using PPIs but without subsequent AMI or CHD, it was shown [16] that longterm PPI use or highdose PPI use increased the risk of firstever AMI in patients (OR 1.56; 95% CI 1.45–1.69) without a history of CHD. The Taiwanese scientists noted that the increased risk of AMI was associated with the use of all PPIs studied (omeprazole, esomeprazole, rabeprazole, pantoprazole and lansoprazole). In a US casecontrol study of 32,793 patients taking PPIs who developed AMI and 127,291 control patients without AMI, individuals who started PPI therapy [17] had an increased risk of MI (adjusted OR (AOR) 2.8; 95% CI 2.63.0).

In a recently published retrospective analysis by Chinese cardiologists [18], data from the US National Health and Nutrition Examination Survey (NHANES) for 20072018 were used. In a cross-sectional analysis of data from 47,713 US adults, PPI use was positively associated with the risk of MI (OR 1.668; 95% CI 1.224–2.273; p <0.001). Subgroup analysis showed that men and smokers were more susceptible to MI risk associated with longterm PPI use [18].

Proton pump inhibitors and arterial hypertension

Japanese and French scientists studied the potential association between PPIs and arterial hypertension (AH) using the WHO pharmacovigilance database

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[19]. The database contained 26,587 reports of AH associated with PPIs (2.3%), predominantly in women (63.3%). A significant reporting odds ratio (ROR) was observed for almost all PPIs in both univariate (ROR 1.32–1.97) and multivariate analyses after adjustment for confounders (adjusted ROR 1.09–1.35). A potential trend indicating a doseeffect relationship was identified: doses below the median were associated with a lower adjusted ROR for AH [19].

In a study by a group of American scientists involving 64,720 menopausal women without CVD or AH at baseline, 28,951 cases of AH were recorded after a mean followup of 8.7 years [20]. PPI use was associated with a 17% increased risk of AH compared with nonusers in the fully adjusted model (HR 1.17; 95% CI 1.08–1.27). Longer PPI use was significantly associated with a gradually increasing risk of AH (HR 1.13; 1.17; 1.28 respectively; p for trend <0.001). The 3year change in mean systolic blood pressure adjusted for multivariate factors significantly increased in new PPI users (+3.39 mm Hg; p = 0.049) compared with those who never used these drugs. Thus, PPI use was associated with an increased risk of developing AH in menopausal women, and the risk showed a significant trend towards increasing with duration of use [20].

Proton pump inhibitors and stroke

Longterm PPI use increases the risk of stroke by raising plasma ADMA levels and reducing NO levels [21]. Neurologists from South Korea, in a multivariate Cox regression analysis, demonstrated an association between longterm PPI use and the development of cerebral small vessel disease and deep white matter hyperintensity, which may be a cause of stroke or cognitive decline (HR 3.453; 95% CI 1.027–9.475; p = 0.045) [22].

In a Danish nationwide retrospective cohort study of 214,998 individuals, over a median followup of 5.8 years, 7,916 cases of IS and 5,608 cases of MI were recorded. The risk of firstever IS (HR 1.13; 95% CI 1.08–1.19) and MI (HR 1.31; 95% CI 1.23–1.39) was elevated in PPI users [23]. High doses of PPIs were associated with an increased incidence of IS (HR 1.31; 95% CI 1.21–1.42) and MI (HR 1.43; 95% CI 1.30–1.57). Longterm PPI use, compared with nonusers, increased the risk of IS by 29% (95% CI 559%) and the risk of MI by 36% (95% CI 773%) over 6 months. H2antihistamine use was not significantly associated with IS (HR 1.02; 95% CI 0.84–1.24) or MI (HR 1.15; 95% CI 0.92–1.43) [23]. In a Taiwanese retrospective nationwide cohort study using 198,148 courses of PPI therapy and control periods without PPI use, PPI use was positively associated with an increased risk of hospitalisation for IS (HR 1.36; 95% CI 1.14–1.620; p=0.001) [24]. In a nested casecontrol analysis, Taiwanese neurologists and gastroenterologists identified 15,378 patients hospitalised for IS and compared them with matched controls (n=15,378); an association was found between PPI use and elevated cerebrovascular risk within 30 days (AOR 1.77; 95% CI 1.45–2.18; p<0.001), within 3190 days (AOR 1.65; 95% CI 1.31–2.08; p<0.001), and within 91180 days (AOR 1.28; 95% CI 1.03–1.59; p=0.025) from the start of PPI therapy to the first IS [24].

In a prospective analysis by Chinese scientists among 492,479 participants from the UK Biobank, over a followup of 3,935,030 personyears, 5,182 cases of stroke were documented [25]. Regular PPI use was associated with a 16% increased risk of stroke compared with nonusers (HR 1.16; 95% CI 1.06–1.27). This result was close to the results of a metaanalysis of nine randomised controlled trials (events/participants 371/26,642; HR 1.22; 95% CI 1.001.50) conducted by the authors. In a metaanalysis by Chinese cardiologists (14 studies) [26], PPI users had a higher risk of stroke (OR 1.22; 95% CI 1.08–1.36), MI (OR 1.23; 95% CI 1.14–1.32), MACE (OR 1.22; 95% CI 1.05–1.40) and cardiovascular death (OR 1.83; 95% CI 1.69–1.98).

Proton pump inhibitors and cardiac arrhythmias

Chinese cardiologists conducted a study to determine the association between PPI treatment and QT interval prolongation in critically ill patients [27]. The study included 24,512 intensive care unit patients. Of these, 11,327 patients received PPIs (group 1), 4,181 received H2antihistamines (group 2), and 6,351 had no acidsuppressive therapy (group 3); the frequency of QT prolongation in the groups was 8.5%, 3.3% and 3.4%, respectively. After adjustment for confounders, PPI use was associated with a higher risk of QT prolongation compared with H2antihistamines (OR 1.66; 95% CI 1.36–2.03) and compared with no acidsuppressive therapy (OR 1.54; 95% CI 1.31–1.82). Two drugs, pantoprazole (OR 2.14; 95% CI 1.52–3.03) and lansoprazole (OR 1.80; 95% CI 1.18–2.76), showed a higher risk of QT prolongation than omeprazole.

Concomitant medications conferred a higher risk of QT prolongation when combined with PPI use.

In a DanishDutch study, it was found that PPI use was associated with an increased risk of outofhospital sudden cardiac arrest (SCA) [28]. The authors identified 46,578 cases of SCA and 232,890 control individuals without a history of SCA. PPIs were used by 8,769 patients with SCA and 21,898 patients without SCA in the control group. Current PPI use increased the odds of SCA compared with nonusers (OR 1.32; 95% CI 1.28–1.37). The risk remained elevated in individuals without registered CHD (OR 1.36; 95% CI 1.31–1.41), without HF (OR 1.33; 95% CI 1.29–1.38) or without any concomitant CVD (OR 1.84; 95% CI 1.70–2.00).

Furthermore, a close association of longterm PPI use with important cardiovascular risk factors such as DM [29] and chronic kidney disease (CKD) [30] has been noted.

Proton pump inhibitors and rhabdomyolysis

During the search for sources addressing PPI adverse effects, several clinical cases reporting the development of rhabdomyolysis in individuals taking PPIs were found. This rare adverse effect has been described with all major representatives of the PPI class: omeprazole, esomeprazole, rabeprazole, pantoprazole and lansoprazole [31, 32]. In the description of the active substances of the main PPI representatives, rhabdomyolysis is not listed among the adverse effects. In cardiological practice, it is known that rhabdomyolysis is a serious adverse reaction to HMGCoA reductase inhibitors (statins) [33]; however, in the "drug interactions" section for the main PPI representatives, the interaction of PPIs with statins is not addressed.

Japanese pharmacologists and gastroenterologists analyzed two databases: the Japanese Medical Data Vision (MDV) and the US FDA Adverse Event Reporting System (FAERS) [34]. Multiple logistic regression analysis of both databases showed a significant association between PPI use and an increased risk of rhabdomyolysis (OR 1.84, 95% CI 1.74–1.95, $p \leqslant 0.01$). H2antihistamine use was not significantly associated with an increased risk of rhabdomyolysis. Pharmacologists from Saudi Arabia also used the FDA FAERS database for the period 20132021 [35]. The authors found 57 reports linking PPIs to rhabdomyolysis out of 3,670 reports for other drugs (including nonstatins). The association between rhabdomyolysis and PPIs was significant in reports both including statins (ROR 2.0; 95% CI 1.5–2.6) and excluding statins (ROR 2.5; 95% CI 1.9–3.2). Chinese pharmacologists in the FDA FAERS database analyzed 1,899 reports with complete patient demographic data [31]. Lansoprazole had the highest ROR—12.67, followed by esomeprazole (11.18), omeprazole (10.27), rabeprazole (10.06) and pantoprazole (9.24). In cases of rhabdomyolysis, PPIs were mainly "concomitant" drugs (>60%), and only a few cases were "primary suspects" (<15%). Rabeprazole showed the lowest mortality rate, while lansoprazole had the highest. American gastroenterologists [36] note that in the development of rhabdomyolysis with PPI use, their interaction with coadministered drugs such as statins may be involved. In patients who recover from an episode of PPIassociated rhabdomyolysis but have no real need to continue PPIs, rechallenge is not advisable. In those with clear indications for continued PPI treatment, PPIs may be resumed, but it is advisable not to prescribe them together with statins.

Discussion

In realworld clinical practice, longterm PPI use refers to their use for more than 4 weeks in gastric diseases (peptic ulcer and functional dyspepsia) and for more than 8 weeks in oesophageal diseases [37]. This review presents data suggesting a possible association between longterm PPI use and the development of MI, AH, stroke and cardiac arrhythmias.

A review by American cardiologists notes that since longterm PPI use may increase the risk of CVD, the benefits of PPIs must be carefully weighed against the potential risks for each patient [38]. Alternative treatments may be used for individuals at high CV risk.

To date, the attitude towards using PPIs for gastrointestinal mucosal protection and prevention of gastrointestinal bleeding during longterm antithrombotic therapy in cardiological practice is controversial. A review by American cardiologists [39] notes that in patients with CVD receiving dual antiplatelet therapy (DAPT), drug interactions between clopidogrel and PPIs may lead to worse cardiovascular outcomes [12]. A multicentre Chinese study [40] included 25,567 patients with acute coronary syndrome (ACS) receiving DAPT. PPIs were prescribed within 24 hours of admission to 63.9% (n=16,332) of patients. A higher

rate of gastrointestinal bleeding was noted in PPI users compared with nonusers (1.0% vs. 0.5%; p<0.001). In a multivariate Cox regression analysis, early PPI use was associated with a 58% increased risk of gastrointestinal bleeding (HR 1.58; 95% CI 1.15–2.18; p=0.005). A South Korean multicentre observational study determined the risk of lower gastrointestinal bleeding and compared this risk between NSAID+PPI users (target cohort, n=24,530) and NSAIDonly users (comparison cohort, n=57,264) [41]. The risk of lower gastrointestinal bleeding was significantly higher in the target cohort (NSAID+PPI) than in patients taking NSAIDs alone (HR 2.843; 95% CI 1.998–4.044; p < 0.001). Similar results were noted in subgroups—elderly patients >65 years (HR 2.737), men (HR 2.963) and women (HR 3.221).

Consensuses of Russian experts on antithrombotic therapy in elderly and senile age [42] and on reducing the risk of gastrointestinal bleeding in patients receiving oral anticoagulants [43] note that a significant drawback of PPIs is their inability to prevent erosiveulcerative lesions of the lower gastrointestinal tract associated with antiplatelet and anticoagulant use. Moreover, PPI use, on the contrary, increases the risk of enteropathy, may enhance damage to the small intestinal mucosa (especially when combined with NSAIDs), and may even provoke lower gastrointestinal bleeding. In this regard, it is advisable to use gastroprotective agents with a mechanism of action different from that of PPIs, for example rebamipide.

Recent reviews have formulated the main principle of PPI therapy safety: prescribing PPIs strictly according to indications (in accordance with clinical guidelines), adhering to short courses and minimal effective doses [44, 45].

Conclusion

The conducted literature analysis suggests a possible association between longterm PPI use and the development of MI, AH, stroke and cardiac arrhythmias. During the review of the literature, an unexpected serious adverse reaction associated with PPI use—rhabdomyolysis—was identified.

This review article indicates the possibility and reality of cardiovascular risk with longterm PPI use, and that this should be taken into account when prescribing PPIs for a long period, especially in comorbid patients. Increasing awareness among physicians and patients about the proper use of PPIs and knowledge of the adverse effects of longterm therapy will optimize the use of these drugs in realworld clinical practice.

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