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# Prolonged utilization of proton pump inhibitors in patients with ischemic and valvular heart disease is associated with surgical treatments, weight loss and aggravates anemia

Marko Boban [a,b,*,1], Marinko Zulj [b], Viktor Persic [a,b], Igor Medved [c], Drazen Zekanovic [a,b], Aleksandar Vcev [b]

[a] Department of Cardiology, University hospital "Thalassotherapia Opatija", Medical Faculty, University of Rijeka, Croatia
[b] Department of Internal Medicine, Medical Faculty "J.J. Strossmayer", University of Osijek, Croatia
[c] Department of Cardiac Surgery, Medical Faculty, University of Zagreb, University hospital centre "Zagreb", Croatia

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ABSTRACT

*Background:* Proton pump inhibitors (PPIs) are among the commonest drugs used nowadays. The aim of our study was to analyze prolonged utilization of proton pump inhibitors in medical therapy of patients with ischemic and valvular heart disease. Secondly, profile of utilization was scrutinized to patient characteristics and type of cardiovascular treatments.
*Methods:* The study included consecutive patients scheduled for cardiovascular rehabilitation 2–6 months after index cardiovascular treatment.
*Results:* Two hundred ninety-four patients (n = 294/604; 48.7%) have been using proton pump inhibitor in their therapy after index cardiovascular treatment. Cardiovascular treatments were powerfully connected with utilization of PPIs; surgery 5.77 (95%-confidence intervals [CI]: 4.05–8.22; $p < 0.001$) and PCI 0.15 (CI: 0.10–0.22; $p < 0.001$). The odds for having proton pump inhibitor in their chronic therapy were increased for atrial fibrillation 1.87 (CI: 1.08–3.23; $p = 0.025$) and decreased for obesity 0.65 (CI: 0.45–0.96; $p = 0.035$); surviving myocardial infarction 0.49 (CI: 0.29–0.83; $p = 0.035$). Multinomial logistic regression controlled for existence of chronic renal disease found no significant association of renal dysfunction and PPI therapy. The existence of anemia was significantly increased in patients taking PPIs than controls; 6.00 (CI: 3.85–9.33; $p < 0.001$). The use of PPI was also associated with worsening of metabolic profile, in part due to decreased utilization of ACE-inhibitors and statins. PPI consumption correlated with age of patients (Rho = 0.216; $p < 0.001$).
*Conclusions:* High proportion of cardiovascular, particularly surgical patients with ischemic and valvular heart disease utilized proton pump inhibitor in prolonged courses. Prolonged courses of PPIs were connected with existence and worsening of red blood count indexes, older age, lesser weight of patients and underutilization of cardioprotective drugs.



## 1. Introduction

Cardiovascular diseases are among the most important global public health burdens [1]. Those are chronic diseases with high and constantly increasing trends of prevalence, as well as the leading cause of death [1]. Aging of population, obesity, poor diet and lifestyle management, along with cigarette abuse cause additional interferences in predicting future perspectives [2]. Significant changes in cardiovascular disease outcomes were attained by lifestyle alternations, invasive treatments and several types of pharmaceuticals [3]. In those circumstances even some well established causative connections from *cardiovascular diseases continuum* become uncertain, which could be seen in entities as obesity paradox, sarcopenic obesity and cardiac cachexia [4,5].

Proton pump inhibitors (PPIs) are among the commonest drugs used today [6]. Those frequently became part of therapy in patients with cardiovascular diseases. Despite their efficiency on heartburn symptoms, healing of peptic ulcers, and treatment and prevention of gastrointestinal bleeding, there are numerous unwanted side-effects existing, making cost–benefit questionable [7]. PPIs suppress gastric acid secretion, causing hypoabsorption of ionic molecules as ferric, magnesium, and calcium [8,9]. Large volume studies found an increased incidence of community acquired pneumonia and *Clostridium difficile*-associated diarrhea [10,11]. On the longer run those could cause

* Corresponding author at: Department of Cardiology, University Hospital Thalassotherapia Opatija, Medical Faculty University of Rijeka, Medical Faculty "J.J. Strossmayer" University of Osijek, Croatia.
*E-mail address:* marcoboban@yahoo.com (M. Boban).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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hypertrophy of gastric mucosa, and changes in gut microbiota, as well as *Helicobacter pylori* infection [12]. PPIs might cause anemia and changes in platelet aggregation tests [13,14]. Heartburn drugs became noticeably prevalent iatrogenic confounder, which can interfere with the clinical course and alternate outcomes of cardiovascular diseases [15,16].

The aim of our study was to systematically analyze prevalence of prolonged utilization, potential side-effects and other clinical connections of PPIs in a cohort of patients scheduled for cardiovascular rehabilitation.

## 2. Methods

Study population included a consecutive sample of patients scheduled for cardiovascular rehabilitation 2–6 months after treatment for ischemic or valvular heart disease. Diagnostics covered medical records from previous treatments, anthropometrics, demographics, echocardiography, conventional laboratory, 12 channel electrocardiography, and echocardiography exam.

The study did not include patients with acute or chronic contraindications for cardiovascular rehabilitation. The most important contraindications were: severe acute illness or decompensated and/or advanced chronic disease, decompensated heart failure, thyroid disorders, unregulated diabetes, metastatic cancer, end stage respiratory and renal disease, hemodynamic instability or severe disorders of rhythms.

*Drug utilization analyses* included prevalence of therapy with: proton pump inhibitor, acetylsalicylate/thienopyridine, warfarin, ACE-inhibitor/angiotensinogen receptor blocker, calcium antagonist, beta blocker, loop diuretic, and antidiabetics (oral or insulin). In general, the use of pharmaceuticals was studied through therapeutic groups, and there were no sub-analyses of particular representatives.

### 2.1. Comorbidities and cardiovascular risk

Medical history included analyses of prevalence for: hypercholesterolemia, arterial hypertension, known diabetes mellitus, glucose intolerance, chronic renal disease (CRD), cigarette smoking status, chronic obstructive pulmonary disease, atherosclerotic process and thrombosis (medical history of clinically evident peripheral artery disease, cerebrovascular stroke, carotid artery stenosis and pulmonary artery embolism), atrial fibrillation, past myocardial infarction, left ventricle systolic dysfunction (cutoff point set at 40%) and history of gastrointestinal bleeding.

## 3. Statistical analyses

Population and studied groups were analyzed with descriptive statistic and presented as a means combined with standard deviations. Population demographic, comorbidities, treatments and other group analyses were calculated with Chi square or Kruskal–Wallis tests accordingly. Data on anthropometrics, laboratory, echocardiography and remainder numeric data were analyzed for differences by Mann–Whitney U test. Connections of PPI utilization with studied clinical parameters were done by Spearman Rho. Odds for PPI utilization according to index cardiovascular treatment were calculated in binomial logistic regression and patients' comorbidities were calculated in polynomial logistic regression model. p value less than 0.05 was considered significant. Statistical analyses were done by an experienced statistician using IBM-SPSS12 v 20 (IBM co, Chicago, IL, USA) and Statistica 10 for Windows (StatSoft inc, Tulsa, OK, USA).

### 3.1. Ethical approval

The study was approved by the ethical committee of our University Hospital. Patients were included after signing the informed consent. The study was performed in accordance with The Declaration of Helsinki and respecting the good clinical practice guidelines. There were no financial compensations for patients or authors.

## 4. Results

### 4.1. Patients

The study included a population of six hundred and four (N = 604) consecutive patients scheduled for cardiovascular rehabilitation. Mean age was 63.5 ± 10.9 years (range 23–87), with 283 (46.9%) in the group older than 65 years. There were more male patients than female; 440 (72.8%):164 (27.2%), respectively. Obesity was found in 193 (32.1%), glucose intolerance 81 (13.4%), diabetes mellitus (treated) 170 (28.1%) and chronic renal disease in 98 (16.3%). Two hundred twenty-four (37.1%) of patients had never smoked, while 177 (29.3%) were active cigarette abusers or recent quitters and 144 (23.8%) had chronic obstructive pulmonary disease. Four hundred twenty-four (70.0%) patients survived non-fatal myocardial infarction. Known atherothrombotic disorder (including history of peripheral artery disease, carotid disease, cerebrovascular stroke or thromboembolism) was found in 179 (29.6%) and 81 (13.4%) had permanent atrial fibrillation. Mean BMI was 28.5 ± 4.0 kg/m$^2$ (18.5–46.0), of which the majority of patients 301 (49.8%) was overweight (BMI range 25–30 kg/m$^2$) and the remaining 112 (18.5%) were of BMI <25 kg/m$^2$. Waist circumference was 101.4 ± 10.2 cm (67.0–134.0), hip circumference 105.8 ± 9.3 cm (76.0–141.0). Most of the laboratory exams were within referral range or in line with chronic comorbidities of steady phase: hematocrit 0.39 ± 0.05 (0.27–0.52), serum glucose 6.7 ± 1.8 mmol/L, triglycerides 1.66 ± 0.86 mmol/L, total cholesterol 4.38 ± 1.74 mmol/L, LDL-cholesterol 2.31 ± 0.99 mmol/L, HDL-cholesterol 0.99 ± 0.43 mmol/L, urea 7.3 ± 2.7 mmol/L and creatinine 106.4 ± 40.5 μmol/L. Mean left ventricle ejection fraction (LVEF) was 48.9 ± 8.2 (range 20.0–65.00), with systolic dysfunction (LVEF ≤ 40%) in 115 (19.0%) of patients.

Ischemic heart disease was existing in 459 (76.0%) of patients, valvular in 92 (15.2%) and combined (ischemic and valvular) in 53 (8.8%). Treatments included 49 (8.1%) conservatively treated myocardial infarctions, 227 (37.6%) percutaneous coronary interventions and 330 (54.6%) surgical procedures.

Medical records showed no cases of gastrointestinal hemorrhage in the studied population for period after baseline cardiovascular treatments. Diagnosis of peptic ulcer disease in between the index cardiovascular event and rehabilitation was documented by endoscopy in 7 patients (1.1%). There were no reports on dyspeptic symptoms by patients or within medical history, no cases of endoscopy confirmed reflux esophagitis and none of the patients was tested for *H. pylori* in the studied period.

### 4.2. Proton pump inhibitor (PPI) utilization

Two hundred ninety-four patients (n = 294/604; 48.7%) have been using proton pump inhibitor in a prolonged course after index cardiovascular treatment. The type of cardiovascular treatment was associated with prolonged utilization of PPIs in binomial logistic regression; surgery 5.77 (95%-CI from 4.05–8.22; p < 0.001) and PCI 0.15 (95%-CI from 0.10–0.22; p < 0.001). Conservatively treated myocardial infarctions were not significantly connected with PPI utilization in studied binomial model.

Prolonged utilization of PPIs was also connected with cardiovascular risk factors; permanent atrial fibrillation 1.87 (95%-confidence intervals [CI] from 1.08–3.23; p = 0.025); obesity 0.65 (95%-CI from 0.45–0.96; p = 0.035); and surviving myocardial infarction 0.49 (95%-CI from 0.29–0.83; p = 0.035). Other studied comorbidities were insignificantly connected with PPIs in studied polynomial logistic regression model.

Analyses of patient characteristics and clinical diagnostics through the groups of PPI utilization are presented in Tables 1 and 2.