ОГЛЯД ЛІТЕРАТУРИ

UDC 616.1-057:616.329-002.2-085
DOI https://doi.org/10.32782/2226-2008-2025-5-10

L. I. Kolotvina https://orcid.org/0000-0001-9660-3786
G. V. Kornovan https://orcid.org/0000-0002-9733-4482
V. I. Synenko https://orcid.org/0000-0003-0210-6776
A. O. Kolotvin https://orcid.org/0000-0001-6384-9667

GASTROESOPHAGEAL REFLUX DISEASE AND CARDIOVASCULAR DISEASES: INTERRELATION AND MUTUAL INFLUENCE (LITERATURE REVIEW)

Odesa National Medical University, Odesa, Ukraine

UDC 616.1-057:616.329-002.2-085

L. I. Kolotvina, G. V. Kornovan, V. I. Synenko, A. O. Kolotvin

GASTROESOPHAGEAL REFLUX DISEASE AND CARDIOVASCULAR DISEASES: INTERRELATION AND MUTUAL INFLUENCE (LITERATURE REVIEW)

Odesa National Medical University, Odesa, Ukraine

Introduction. The work is dedicated to the problem of comorbidity with cardiovascular disease and gastroesophageal reflux disease.

Objective. Analyze the information in current literary and electronic resources regarding the clinical features of the current history of heart failure and illness of the cardiovascular system.

Materials and methods. An analysis of scientific information was carried out from the following databases: Scopus, Web of Science, MedLine, PubMed, Google Scholar, Global Health, ResearchGate, as well as WHO, Ministry of Health of Ukraine and other Internet resources.

Results. The work presents a review of the current scientific literature on the problem of interconnection and interrelation of the cardiovascular system and illness of the cardiovascular system. Some of the manifestations associated with reflux disease include transient disturbances in heart rhythm and conduction, usually supraventricular extrasystole and atrial fibrillation. Experts note that gastroesophageal reflux is a major trigger for arrhythmia. The problem of the connection between gastroesophageal reflux disease and ischemic heart disease is even relevant, which will require, in case of pain syndrome in the chest, to carry out detailed treatment of the patient to identify the pain, both on the side of the heart and on the side to the walker. It is also necessary to ensure the presence of causal links in the presence of gastroesophageal reflux disease and arterial hypertension.

Conclusion. Obvious comorbidity is associated with significant diagnostic difficulties and will require individual comprehensive treatment of such patients. The data expands the knowledge of the more common clinical features of esophagocardial interaction and is the basis for optimizing medical tactics for this category of patients.

Keywords: gastroesophageal reflux disease, atrial fibrillation, ischemic heart disease, arterial hypertension.

УДК 616.1-057: 616.329-002.2-085

Л. І. Колотвіна, Г. В. Корнован, В. І. Синенко, А. О. Колотвін

ГАСТРОЕЗОФАГЕАЛЬНА РЕФЛЮКСНА ХВОРОБА ТА ЗАХВОРЮВАННЯ СЕРЦЕВО-СУДИННОЇ СИСТЕМИ: ВЗАЄМОЗВ'ЯЗОК І ВЗАЄМОВПЛИВ (ОГЛЯД ЛІТЕРАТУРИ)

Одеський національний медичний університет, Одеса, Україна

Серед частих проявів, асоційованих із рефлюксною хворобою, є транзиторні порушення ритму серця та провідності. Експерти відмічають, що гастроезофагеальний рефлюкс виступає безпосереднім тригером виникнення аритмії. Проблема зв'язку ГЕРХ та ішемічної хвороби серця є дуже актуальною, що потребує за наявності больового синдрому в грудній клітці проводити детальне обстеження хворого для виявлення джерела болю як з боку серця, так і з боку стравоходу. Потрібно також враховувати наявність причинно-наслідкових зв'язків за поєднання ГЕРХ та артеріальної гіпертензії. Наявна коморбідність пов'язана з певними діагностичними труднощами, потребує індивідуального комплексного обстеження таких пацієнтів.

Ключові слова: гастроезофагеальна рефлюксна хвороба, фібриляція передсердь, ішемічна хвороба серця, артеріальна гіпертензія.

Introduction

In recent years, the problem of comorbidity of diseases, namely the simultaneous coexistence of several pathologies in a single patient, has been increasingly discussed. This condition is a significant factor that aggravates the overall health of the patient, complicates the diagnosis of each disease, increases the number and severity of complications, and affects the choice of therapeutic strategy [1]. Experts note that comorbidity is a global medical and socio-economic issue that significantly affects the life prognosis of each patient [2]. Today, in real clinical practice, there are very few patients suffering from a single

© L. I. Kolotvina, G. V. Kornovan et at., 2025

Стаття поширюється на умовах ліцензії

disease, particularly in its classic course. It has been proven that comorbid conditions often worsen the course of the primary disease, contribute to its chronicity, and are a cause of disability and premature death [3]. This situation requires additional diagnostic and treatment approaches for this category of patients.

The cardiovascular system is one of the key systems in the human body, participating in the functioning of all organs and systems. Therefore, its condition should be especially considered in the context of comorbidity. The relationship and mutual influence between cardiovascular diseases and gastrointestinal tract disorders, particularly gastroesophageal reflux disease (GERD), have long been known. However, this issue remains relevant to practical medicine and requires further in-depth study.

Objective. To analyze information from modern literary and electronic resources regarding the clinical features of the combined course of gastroesophageal reflux disease and cardiovascular diseases.

Materials and Methods

A review of scientific information was conducted using databases such as Scopus, Web of Science, MedLine, PubMed, Google Scholar, Global Health, ResearchGate, as well as resources from WHO, the Ministry of Health of Ukraine, and other internet resources.

Research results and their discussion

One of the most common situations is the comorbidity of cardiovascular diseases and GERD, which affects, according to various authors, an average of 10% to 20% of the adult population in economically developed countries [4; 5]. Currently, there are isolated reports indicating that, based on surveys, the prevalence of GERD among adults in Ukraine averages 30%, whereas epidemiological data show a rate of 11.1% [6]. According to current concepts, this comorbidity is primarily due to shared risk factors, including unbalanced nutrition, smoking, a sedentary lifestyle, excess body weight, and visceral obesity, sleep disorders and the presence of obstructive sleep apnea syndrome [7; 8; 9]. Researchers have observed that patients with GERD and visceral obesity experience increased intra-abdominal pressure, heightened gastroesophageal gradient due to increased fat tissue volume, and elevated levels of the pro-inflammatory cytokine interleukin-6, along with decreased levels of the anti-inflammatory cytokine interleukin-10 [10]. It is now known that both diseases share common pathogenic mechanisms, including immune dysfunction [11], and general metabolic disorders [12; 13]. According to recent data, metabolic syndrome, one of the components of which is visceral obesity, the fat of which is metabolically active [14], is proposed to be considered as an inflammatory condition in which there is an increase in the levels of interleukin-1β and interleukin-6, interleukin-8, tumor necrosis factor-alpha, and nuclear factor kappa-β, all of which can impair the function of the lower esophageal sphincter and exacerbate gastroesophageal reflux [15]. Studies show a significant link between obesity and the severity of symptoms, the rate of progression of GERD, and the development of complications, namely Barrett's esophagus, esophageal cancer [16; 17; 18].

Among the frequent manifestations associated with reflux disease are transient heart rhythm and conduction disorders, primarily supraventricular extrasystole and atrial fibrillation (AF) [9]. Heart rhythm is a crucial indicator reflecting changes in autonomic homeostasis, with disturbances often serving as an early prognostic sign of various diseases [19]. Over the past few decades, substantial evidence has accumulated linking GERD to an increased risk of developing AF [19]. Researchers emphasize that gastroesophageal reflux can act as a direct trigger for arrhythmias [20; 21]. Several pathophysiological mechanisms explaining this link have been identified. Specialists note that GERD can disrupt the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system, with esophageal refluxate stimulating reflex zones in the distal esophagus, thereby creating an arrhythmogenic substrate for the onset and maintenance of AF [22; 23]. Many researchers consider excessive vagus nerve stimulation as one of the key triggers for supraventricular rhythm disturbances in GERD [22; 24; 25]. Other mechanisms of AF development in this comorbidity include local inflammation of the left atrial wall during reflux esophagitis [26] and mechanical irritation due to the anatomical proximity of the left atrium and esophagus [27]. Studies show that treating GERD with proton pump inhibitors (PPIs) in cases of paroxysmal AF reduces the frequency of paroxysms [25; 28]. Researchers believe that the mechanism of action of PPIs extends beyond their acid-suppressive effects [25; 28]. There is speculation that PPIs may influence ATF-dependent potassium channels in the heart [29], and their beneficial effect may also be attributed to their antioxidant and anti-inflammatory properties [28]. However, some studies demonstrate insufficient evidence of the effectiveness of PPIs in this comorbidity. For instance, research by Odashiro K. et al. reported a reduction in the severity and duration of AF symptoms but found no significant changes in the number of paroxysms [30], indicating the need for further investigation.

Diagnosis of chest pain is a crucial issue in esophagocardiac interaction. Studies indicate that in 10–15% of GERD patients, chest discomfort is the sole manifestation of the diseases [31]. The association between GERD and coronary heart disease (CHD) is increasingly being recognized. It is important to consider that esophageal disorders and coronary artery disease can coexist in the same patient, exacerbating each other's course. The presence of esophageal pathology does not rule out cardiovascular diseases, including CHD, in a patient. Therefore, detailed examinations are necessary to identify the source of chest pain, including potential esophageal origins. Research indicates that up to 40% of CHD patients have lesions in the gastroesophageal region, while 62.7% of patients with gastrointestinal disorders also have concomitant cardiovascular diseases, predominantly CHD [31]. Data from one analysis show that GERD can be considered as one of the risk factors for CHD [32]. Endothelial dysfunction is recognized as a crucial pathogenetic mechanism in the development of CHD. Data show that patients with both GERD and CHD exhibit elevated levels of endothelin-1, pro-inflammatory cytokines, and lipid peroxidation products, as well as decreased nitric oxide metabolites, contributing to the

progression of endothelial dysfunction [33]. These changes lead to microcirculatory disturbances in both the myocardium and the esophageal mucosa, resulting in decreased mucosal resistance and lower esophageal sphincter dysfunction [34; 35]. It is known that determining the coronary calcium index is one of the important non-invasive methods for diagnosing coronary atherosclerosis. A study spanning over 14 years demonstrated that patients with more severe GERD were significantly more likely to have higher coronary calcium index levels [35], emphasizing the need for a comprehensive examination of GERD patients with multiple risk factors. The comorbidity of CHD and GERD is characterized by mutual aggravation, alterations in clinical presentation, and atypical manifestations of both diseases [6]. Over recent decades, substantial evidence has accumulated confirming that reflux can trigger angina attacks. Researchers have noted that as the frequency of reflux episodes increases, the threshold for angina attacks decreases, the duration of ischemic episodes extends, and the frequency of pain-free ischemia episodes rises [36]. Studies indicate that irritation of the esophageal mucosa by refluxate can cause reflex coronary artery spasms, significantly impairing coronary blood flow [37]. At the same time, myocardial ischemia may worsen esophageal motility and increase the frequency of lower esophageal sphincter relaxation episodes, thereby promoting GERD progression [32]. Esophagocardiac monitoring of patients with combined CHD and GERD has revealed correlations between myocardial ischemic episodes on ECG, heartburn episodes, and pathological reflux with ST-segment depression [6]. Observations also show that in 30–40% of patients with retrosternal pain, coronary angiography reveals normal coronary arteries [31; 37]. It is important to emphasize that some studies indicate a significantly higher risk of developing gastroesophageal reflux in patients after myocardial infarction, acute cerebrovascular accident [38], at the same time, researchers note an increased relative risk of acute myocardial infarction in patients with GERD [39; 40], particularly in the 40–60 age group [41]. Naturally, the comorbidity of GERD and CHD is most common in elderly patients [6]. Data suggest that the frequency of hiatal hernia increases with age, contributing not only to the development and worsening of GERD but also potentially impairing coronary blood flow due to mechanical pressure on the left atrium [42].

One of the common clinical situations in everyday medical practice is the combination of GERD and arterial hypertension (AH). Recent studies confirm a causal relationship in this comorbidity [43]. Researchers emphasize that in patients with both AH and GERD, the clinical manifestations of the diseases change. Compared to isolated AH, these patients report a greater number and variety of symptoms, such as dizziness, frequent palpitations, and heart irregularities, whereas symptoms like severe heartburn and epigastric pain are less common than in patients with isolated GERD [44]. In this comorbidity, especially in patients with visceral obesity, there is an increase in average daily systolic and diastolic blood pressure levels [44], predominantly at night, and greater variability in blood pressure throughout the day [45; 46]. However, some studies suggest that compared to isolated AH, the course of hypertension in combination with GERD may be more favorable [47]. For example, indicators of left ventricular hypertrophy were significantly higher in patients with isolated AH than in those with combined AH and GERD [45].

Recent years have seen increasing evidence of a causal link between acid reflux and a higher risk of cerebrovascular disorders [40; 48].

The problem of adequate and safe therapy for patients with esophagocardiac comorbidity is becoming particularly relevant. It should be taken into account that the use of nitrates, calcium antagonists, and beta-blockers for the treatment of cardiac pathology, may reduce lower esophageal sphincter tone and provoke pathological reflux, thereby worsening GERD symptoms [27; 33]. Additionally, the use of antithrombotic agents for secondary prevention can cause complications not only in the stomach and intestines but also in the esophagus [49]. The safety of prokinetic drugs is also a pressing issue. It is known that the use of prokinetic agents such as cisapride, domperidone, and tegaserod is associated with adverse cardiovascular safety profiles due to QT interval prolongation and drug-induced arrhythmias [50].

Conclusions

Based on the review of recent scientific publications, it can be concluded that in recent years, significant data have been accumulated on the relationship and mutual influence of GERD and cardiovascular diseases. These findings highlight the relevance and importance of this issue. The presence of comorbidity presents specific diagnostic challenges, requiring individualized and comprehensive examinations of such patients. It necessitates not only the assessment of the functional state of the cardiovascular system but also an evaluation of the esophageal mucosa, its motility, and the tone of the lower esophageal sphincter. These data enhance the understanding of clinical esophagocardiac interactions among family physicians, gastroenterologists, and cardiologists and serve as a foundation for optimizing treatment strategies for this patient category.

BIBLIOGRAPHY

1. Chamberlain AM, Alonso A, Noseworthy PA, et al. Multimorbidity in patients with atrial fibrillation and community controls: A population-based study. *J Multimorb Comorb*. 2024 Dec 21; 14: 26335565241310281. DOI: 10.1177/26335565241310281.
2. Tan MMC, Barbosa MG, Pinho PJMR, et al. Determinants of multimorbidity in low- and middle-income countries: A systematic review of longitudinal studies and discovery of evidence gaps. *Obes Rev*. 2023 Feb; 25(2): e13661. DOI: 10.1111/obr.13661.
3. Abrahamovych O, Fayura O, Abrahamovych U. Komorbidnist: suchasnyy pohlyad na problemu; klasyfikatsiya (pershe povidomlennya). [Comorbidity: a Modern View on the Problem; Classification (first notice)]. *Lviv clinical bulletin*. 2015; 4(12): 56–64. https://doi.org/10.25040/lkv2015.04.056. (In Ukrainian).

4. Marabotto E, Pasta A, Calabrese F, et al. The Clinical Spectrum of Gastroesophageal Reflux Disease: Facts and Fictions. *Visc Med*. 2024 Oct; 40(5): 242–249. DOI: 10.1159/000536583.5.
5. Kashyrtseva OM, NovokhatniaA Ye, Khomenko LO, Oparin AA, Oparina TM**.** EndotheliaL dysfunction and gastroesophageal reflux disease: study of common pathogenetic mechanisms and ways of correction. *Clinical and preventive medecine*. 2024; 2: 75–82. https://doi.org/10.31612/2616-4868.2.2024.10. (In Ukrainian).
6. Prikhodko VYu, Moreva DYu. Peculiarities of gastroesophageal reflux disease in elderly people. *Problemy starinnia ta dovholittia*. 2015; 24(1): 58–77. http://old.geront.kiev.ua/library/psid/t24/n1/Prikhodko.pdf. (In Ukrainian).
7. Fadieienko GD, Nesen AO, Krakhmalova OO, Izmailova OV. Mechanisms of formation of comorbidity of gastroesophageal reflux disease and coronary heart disease. *Modern Gastroenterology*. 2018; 3(101): 7–13. https://doi.org/10.30978/MG-2018-3-7. (In Ukrainian).
8. Gesualdo M, Scicchitano P, Carbonara S, et al. The association between cardiac and gastrointestinal disorders: causal or casual link? *J Cardiovasc Med (Hagerstown)*. 2016 May; 17(5): 330–8. DOI: 10.2459/JCM.0000000000000351.
9. Liang J, Tang L, Yang J, Li Y, Yang X, Hou C. Gastroesophageal reflux disease and risk for arrhythmias: a Mendelian randomization analysis. *Front Cardiovasc Med.* 2024 Jul 29; 11: 1411784. DOI: 10.3389/fcvm.2024.1411784.
10. Stepanov YuM, Mosiychuk LM, Tatarchuk OM, Shevtsova OM, Petishko OP. Vplyv vistseralnoho ozhyrinnya na tsytokinovu ta hormonalnu rehulyatsiyu u patsiyentiv iz hastroezofahealnoyu reflyuksnoyu khvoroboyu [Effects of visceral obesity on cytokine and hormonal regulation in patients with gastroesophageal reflux disease]. *Gastroenterologìa*. 2023; 3(57): 19–24. https://doi.org/10.22141/2308-2097.57.3.2023.551. (In Ukrainian).
11. Lei WY, Wang JH, Wen SH, et al. Risk of acute myocardial infarction in patients with gastroesophageal reflux disease: A nationwide population-based study. *PLoS One*. 2017 Mar 20; 12(3): e0173899. DOI: 10.1371/journal.pone.0173899.
12. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*. 2018; 67(3): 430–440. DOI: 10.1136/gutjnl-2016–313589.
13. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018 Feb 26; 20(2): 12. DOI: 10.1007/s11906-018-0812-z.
14. Zhuravlyova LV, Filonenko MV. Gastroesophageal reflux disease in patients with metabolic syndrome: the peculiarities of clinical course and the modern approaches to treatment. *Modern Gastroenterology*. 2018; 4: 90–95. https://doi.org/10.30978/MG-2018-3-90. (In Ukrainian).
15. Loke SS, Yang KD, Chen KD, Chen JF. Erosive esophagitis associated with metabolic syndrome, impaired liver function, and dyslipidemia. *World J Gastroenterol*. 2013 Sep 21; 19(35): 5883–8. DOI: 10.3748/wjg.v19.i35.5883.
16. Bou Daher H, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: The burning questions. *World J Gastroenterol*. 2019 Sep 7; 25(33): 4805–4813. DOI: 10.3748/wjg.v25.i33.4805.
17. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global Prevalence and Risk Factors of Gastroesophageal Refux Disease (GORD): Systematic Review with Meta-analysis. *Sci Rep*. 2020; 10(1): 5814. DOI: 10.1038/s41598-020-62795.
18. Fu S, Xu M, Zhou H, Wang Y, Tan Y, Liu D. Metabolic syndrome is associated with higher rate of gastroesophageal reflux disease: a meta-analysis. *Neurogastroenterol Motil*. 2022 May; 34(5): e14234. DOI: 10.1111/nmo.14234.
19. Stepanov YuM, Zyhalo EV. Indices of heart rate variability for estimation of adaptive processes and stress resistance in gastroenterology practice (using up-to-date technology of precise-diagnosis). *Gastroenterologìa*. 2020; 54(2): 113–123. DOI: 10.22141/2308-2097.54.1.2020.206230. (In Ukrainian).
20. Huang CC, Chan WL, Luo JC, et al. Gastroesophageal reflux disease and atrial fibrillation: a nationwide population-based study. *PLoS One*. 2012; 7(10): e47575. DOI: 10.1371/journal.pone.0047575.
21. Wang L, Lu YW. Gastroesophageal reflux disease may causally associate with the increased atrial fibrillation risk: evidence from two-sample Mendelian randomization analyses. *Front Cardiovasc Med*. 2024 Jun 3; 11: 1393383. DOI: 10.3389/fcvm.2024.1393383.
22. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J*. 2015; 79(3): 495–502. DOI: 10.1253/circj.CJ-15-0138.
23. Floria M, Bărboi O, Grecu M, Cijevschi Prelipcean C, Balan G, Drug VL. Atrial fibrillation and sympathovagal balance in patients with gastroesophageal reflux disease. *Turk J Gastroenterol*. 2017 Mar; 28(2): 88–93. DOI: 10.5152/tjg.2017.16540.
24. Linz D, Hohl M, Vollmar J, Ukena C, Mahfoud F, Böhm M. Atrial fibrillation and gastroesophageal reflux disease: the cardiogastric interaction. *Europace*. 2017 Jan; 19(1): 16–20. DOI: 10.1093/europace/euw092.
25. Mohamed A, Ochoa Crespo D, Kaur G, et al. Gastroesophageal Reflux and Its Association with Atrial Fibrillation: *A Traditional Review. Cureus*. 2020, September 11; 12(9): e10387. DOI: 10.7759/cureus.10387.
26. Gutierrez A, Van Wagoner DR. Oxidant and Inflammatory Mechanisms and Targeted Therapy in Atrial Fibrillation: An Update. *J Cardiovasc Pharmacol*. 2015 Dec; 66(6): 523–9. DOI: 10.1097/FJC.0000000000000313.
27. Maruyama T, Fukata M, Akashi K. Association of atrial fibrillation and gastroesophageal reflux disease: Natural and therapeutic linkage of the two common diseases. *J Arrhythm*. 2018 Oct 12; 35(1): 43–51. DOI: 10.1002/joa3.12125.
28. Lin K, Chen X, Zhang L, Wang Y, Shan Z. Proton pump inhibitors as also inhibitors of atrial fibrillation. *Eur J Pharmacol.* 2013 Oct 15; 718(1–3): 435–40. DOI: 10.1016/j.ejphar.2013.07.043. Epub 2013 Aug 21. PMID: 23973848.
29. Jeremic N, Petkovic A, Srejovic I, Zivkovic V, Djuric D, Jakovljevic V. Effects of ischemia and omeprazole preconditioning on functional recovery of isolated rat heart. *Rev Bras Cir Cardiovasc*. 2015; 30: 266–275. DOI: 10.5935/1678–9741.20150020.
30. Odashiro K, Yokoyama T, Yoda S, et al. Prevalence of gastroesophageal reflux disorder in arrhythmic patients and adjunctive effects of proton pump inhibitors on comorbid atrial fibrillation. I*nt. J. Basic Clin. Pharmacol*. 2015; 4: 644–650. https://doi.org/10.18203/2319-2003.ijbcp20150365.

31. Prikhodko VYu, Moreva DYu. Features of the course and treatment of hypertension in combination with chronicis chemic heart disease in patients with gastroesophagel reflux disease. *Famili medecine.* 2016; 1(63): 65–70. https://doi.org/10.30841/2307-5112.1(63).2016.102165. (In Ukrainian).
32. Chen CH, Lin CL, Kao CH. Association between gastroesophageal reflux disease and coronary heart disease: A nationwide populationbased analysis. *Medicine (Baltimore)*. 2016; 95(27): e4089. DOI: 10.1097/MD.0000000000004089.
33. Jagirdhar GSK, Bains Y, Surani S. Investigating causal links between gastroesophageal reflux disease and essential hypertension. *World J Clin Cases*. 2024 May 16; 12(14): 2304–2307. DOI: 10.12998/wjcc.v12.i14.2304.
34. Oparin A, Vnukova A. The Role of Endothelial Dysfunction in the Mechanism of Gastroesophageal Reflux Disease Development in Patients with Ischemic Heart Disease. *Acta Clin Croat*. 2017 Dec; 56(4): 635–639. DOI: 10.20471/acc.2017.56.04.08.
35. Song JH, Kim YS, Choi SY, Yang SY. Association between gastroesophageal reflux disease and coronary atherosclerosis. *PLoS One*. 2022 May 20; 17(5): e0267053. DOI: 10.1371/journal.pone.0267053.
36. Liu Y, He S, Chen Y, et al. Acid reflux in patients with coronary artery disease and refractory chest pain. *Intern Med*. 2013; 52(11): 1165–71. DOI: 10.2169/internalmedicine.52.0031.
37. Kato H, Ishii T, Akimoto T, Urita Y, Sugimoto M. Prevalence of linked angina and gastroesophageal reflux disease in general practice. *World J Gastroenterol*. 2009 Apr 14; 15(14): 1764–8. DOI: 10.3748/wjg.15.1764.
38. Jansson C, Nordenstedt H, Wallander MA, et al. Severe symptoms of gastro-oesophageal reflux disease are associated with cardiovascular disease and other gastrointestinal symptoms, but not diabetes: a population-based study. *Aliment Pharmacol Ther*. 2008 Jan 1; 27(1): 58–65. DOI: 10.1111/j.1365-2036.2007.03537.x.
39. Wu Q, He C, Huang W, et al. Gastroesophageal reflux disease influences blood pressure components, lipid profile and cardiovascular diseases: Evidence from a Mendelian randomization study. *J Transl Int Med*. 2024 Nov 6; 12(5): 510–525. DOI: 10.1515/jtim-2024-0017.
40. Chen S, Chen Z, Jiang X, Lin C, Ji J. Modifiable risk factors mediate the effect of gastroesophageal reflux disease on stroke and subtypes: A Mendelian randomization study. *J Stroke Cerebrovasc Dis.* 2024 Apr; 33(4): 107612. DOI: 10.1016/j.jstrokecerebrovasdis.2024.107612.
41. Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA. Is there any association between myocardial infarction, gastroesophageal reflux disease and acidsuppressing drugs? *Aliment Pharmacol Ther.* 2003 Nov 15; 18(10): 973–8. DOI: 10.1046/j.1365-2036.2003.01798.
42. Carmona-Puerta R, Pérez-Sanchez D, Pichardo-Ureña JM, Rodríguez-Monteagudo JL, Lorenzo-Martínez E. The cardiovascular effects of large hiatal hernias: a narrative review of cases and studies. *Postgrad Med.* 2024 May; 136(4): 358–365. DOI: 10.1080/00325481.2024.2360886.
43. Wei N, Liu MH, Song YH. Causal associations between gastroesophageal reflux disease and essential hypertension: A bidirectional Mendelian randomization study. *World J Clin Cases*. 2024 Feb 16; 12(5): 880–890. DOI: 10.12998/wjcc.v12.i5.880.
44. Gridnyev AE. Comparative clinical and biochemical characteristics of hypertension and its comorbidity with gastroesophageal reflux disease. *Ukrainskyi terapevtychnyi zhurnal.* 2016; (2): 39–45. http://nbuv.gov.ua/UJRN/UTJ_2016_2_7. (In Russian).
45. Prikhodko VYu, Moreva DYu. Feauturies of the course and treatment of hypertension in combination with chronicis ichemic heart disease in patients with gastroesophagel refluxdisease. Role of proton pump inhibitors test in the diagnosis and treatment of different forms of GERD. *Famili medecine.* 2016; 4: 75–80. https://family-medicine.com.ua/2412-8708/article/view/248527/249650. (In Russian).
46. Li ZT, Ji F, Han XW, Wang L, Yue YQ, Wang ZG. The Role of Gastroesophageal Reflux in Provoking High Blood Pressure Episodes in Patients with Hypertension. *J Clin Gastroenterol.* 2018 Sep; 52(8): 685–690. DOI: 10.1097/MCG.0000000000000933.
47. Gridnyev AE. Features of the daily profile of arterial pressure and geometry of the left ventricle in patients with a combination of gastroesophageal reflux disease and hypertension. *Ukrainskyi terapevtychnyi zhurnal.* 2015; (4): 40–46. http://nbuv.gov.ua/UJRN/UTJ_2015_4_6. (In Russian).
48. Meng D, Zhang X, Yu W, et al. Association between gastroesophageal reflux disease and stroke: a bidirectional Mendelian randomization study. *Front Neurol.* 2024 Jan 23; 14: 1295051. DOI: 10.3389/fneur.2023.1295051.
49. Sohail R, Mathew M, Patel KK, et al. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: *A Narrative Review. Cureus.* 2023 Apr 3; 15(4): e37080. DOI: 10.7759/cureus.37080.
50. Giudicessi JR, Ackerman MJ, Camilleri M. Cardiovascular safety of prokinetic agents: A focus on drug-induced arrhythmias. *Neurogastroenterol Motil*. 2018 Jun; 30(6): e13302. DOI: 10.1111/nmo.13302.

Надійшла до редакція 25.05.2025
Прийнята до друку 02.12.2025
Електронна адреса для листування larisa.kolotvina@ukr.net