International Journal of General Medicine Dovepress

Open Access Full Text Article REVIEW

Histamine H2 Receptor Antagonists in the Treatment and Prevention of Heart Failure

Dan Wang[1], Hailan Chen[1,*], Yunhao Luo[2,*]

[1]Department of Cardiology, The First People's Hospital of Shuangliu District (West China Airport Hospital, Sichuan University), Chengdu, People's Republic of China; [2]Department of Critical Care Medicine, Chengdu First People's Hospital, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hailan Chen; Yunhao Luo, Email 332489992@qq.com; 496800249@qq.com

Abstract: Despite advancements in the treatment of heart failure (HF) and modest improvements in survival rates over the past few decades, mortality rate remains significantly high. HF not only imposes a significant economic burden on patients' families but also presents a substantial challenge to society at large. Therefore, effective treatment and prevention strategies are crucial. Numerous studies have demonstrated that histamine H2 receptor antagonists (H2RAs) can benefit patients with HF through various mechanisms. These mechanisms encompass promoting sodium and water excretion, vasodilation, enhancing cardiac output, reducing levels of inflammatory cytokines, improving ventricular remodeling, and reducing mortality rate. Additionally, H2RAs exert beneficial effects on typical risk factors and may prevent the onset of HF. This review aims to elucidate the mechanisms underlying the treatment and prevention of HF using H2RAs. For patients requiring either prevention or management of HF, and who concurrently have acid-related diseases, H2RAs may represent a suitable therapeutic option.

Keywords: histamine H2 receptor antagonists, heart failure, prevention, treatment

Introduction

Heart failure (HF) is a syndrome characterized by symptoms such as dyspnea, ankle swelling, and fatigue, accompanied by signs including elevated jugular venous pressure, pulmonary crackles, and peripheral edema. It arises due to structural or functional abnormalities of the heart that can result in increased intracardiac pressure or reduced cardiac output at rest or during stress.[1] Chronic HF affects approximately 2% of adults globally. HF prevalence varies with age, being less than 2% in individuals under 60 and exceeding 10% in those aged 75 and older. Despite advancements in the treatment of HF, the mortality rate remains significantly high. The mortality rate for patients with stable HF is approximately 6%–7% per year. In contrast, the mortality rate for hospitalized patients experiencing acute HF can reach 25% or higher annually. The high incidence of HF, coupled with poor clinical outcomes and significant healthcare costs, underscores that this condition remains a critical public health concern.[2] There are numerous factors involved in the occurrence and progression of HF. Currently, the widely recognized mechanisms encompass neuroendocrine mechanisms, ventricular remodeling, and others. In recent years, the notion that neuroinflammation (ie, neuroimmune cross-talk) could serve as a key driver of disease progression has garnered significant attention and research.[3] The core of HF treatment is to intervene in its pathophysiological mechanism, with the aim of preventing the onset of HF, effectively alleviating symptoms and prolonging patient survival. Recent advances in the treatment of HF include angiotensin receptor-neprilysin inhibitors, cardiac resynchronization therapy, and sodium-glucose cotransporter 2 inhibitors, as well as implantable hemodynamic monitors and left atrial decompression devices. Furthermore, these non-pharmacological approaches, such as dietary interventions, exercise programs, management of sleep-disordered breathing, treatment of mood disorders, and medication use management, are receiving increasing attention.[4,5] Beta blockers are regarded as the cornerstone of treatment for this condition.[6] However, caution should be exercised when administering beta blockers to patients with severe asthma, acute exacerbations of chronic obstructive pulmonary disease, atrioventricular block, and other related conditions, as their use may even be contraindicated in these situations.[7]

Received: 17 October 2024
Accepted: 6 December 2024
Published: 11 December 2024

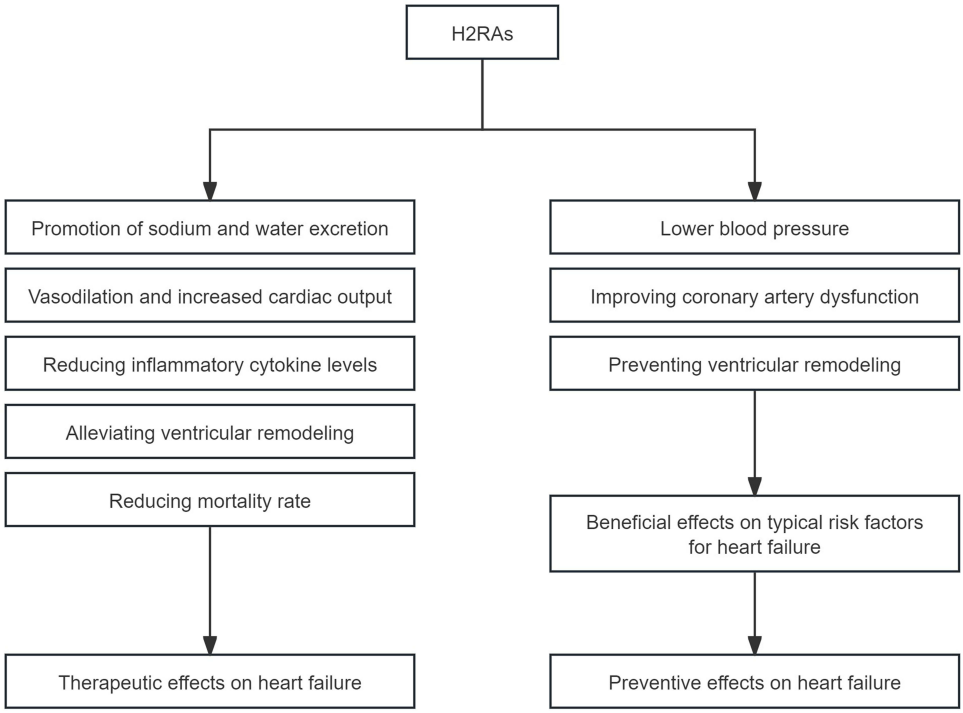

Figure 1 Mechanisms of H2RAs in the treatment and prevention of HF.

Histamine H2 receptor antagonists (H2RAs) competitively inhibit H2 receptors, resulting in a significant reduction in gastric acid secretion. These agents are primarily utilized in the management of gastric acid-related disorders, such as gastric ulcers and reflux esophagitis.[8] Recent studies have demonstrated that H2RAs alleviate symptoms and extend survival in patients with HF. This is achieved through multiple mechanisms, including the promotion of sodium and water excretion, vasodilation, increased cardiac output, reduction of inflammatory cytokine levels, improvement in ventricular remodeling, and reducing mortality rate. Furthermore, H2RAs may exert beneficial effects on risk factors associated with HF, thereby contributing to its prevention. The mechanisms of H2RAs in the treatment and prevention of HF are illustrated in Figure 1. Therefore, for patients who require both the prevention or treatment of HF and have acid-related diseases, H2 receptor antagonists (H2RAs) may represent a suitable therapeutic option.

Promotion of Sodium and Water Excretion

HF is an edematous condition characterized by abnormal hemodynamics and impaired renal excretion, leading to the retention of salt and water. The most prevalent symptom in patients with HF is dyspnea, which arises from the impaired cardiac pump function. This cardiac dysfunction results in retrograde blood flow into the lungs, causing pulmonary congestion. Concurrently, due to the decreased cardiac pumping capacity, fluid accumulation in body tissues manifests as peripheral edema. The alleviation of HF symptoms is predominantly accomplished through diuresis, which helps achieve and maintain optimal blood volume in patients experiencing volume overload.[1] Atrial natriuretic peptide (ANP) possesses the ability to enhance glomerular filtration rate, facilitate sodium and water excretion, leading to reducing blood volume and lowering blood pressure.[9] Patients with HF usually exhibit significant deficiencies in ANP levels along with a decreased renal response to ANP, which can result in sodium and water retention.[10] Cardiac histamine primarily originates from cardiac mast cells.[11] Histamine attenuates the release of ANP through the H2 receptor-cAMP signaling via PKA-dependent and PKA-independent pathways. Histamine binding to histamine H2 receptors, rather than histamine H1 receptors, leads to a decrease in the release of ANP.[12] H2RAs selectively inhibit the interaction of histamine with the H2 receptors on cardiomyocytes, thereby enhancing ANP secretion from these cells. This mechanism subsequently promotes the excretion of sodium and water.[13]

Vasodilation and Increased Cardiac Output

HF is characterized by hemodynamic disturbances, encompassing peripheral vascular constriction and a reduction in cardiac output.[1] ANP promotes vasodilation by activating natriuretic peptide receptor 1 on vascular smooth muscle cells.[14] Sugiyama et al conducted experiments on rats and discovered that lafutidine enhanced neuro-mediated vasodilation through modulating the function of capsaicin-sensitive calcitonin gene-related peptide neuropeptide-1 receptors.[15] H2RAs have the potential to enhance coronary vasodilation, augment myocardial contractility, and improve cardiac pumping fraction through the stimulation of ANP release.[9]

Reducing Inflammatory Cytokine Levels

HF is closely associated with inflammatory syndromes. Elevated levels of local and circulating inflammatory cytokines lead to tissue edema and increased vascular permeability, while a persistent inflammatory state may result in myocardial cell injury and structural remodeling of the heart, further exacerbating HF.[16,17] Roxatidine has been shown to inhibit the production of prostaglandin E(2), nitric oxide, and histamine in a dose-dependent manner. Additionally, it downregulates the expression of cyclooxygenase-2, inducible nitric oxide synthase, as well as histidine decarboxylase at both protein and mRNA levels. Furthermore, roxatidine reduces the production and expression of vascular endothelial growth factor along with pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6. Electrophoretic migration analysis combined with reporter gene assays demonstrated that roxatidine diminishes DNA binding activity and transcriptional activity of nuclear factor κB induced by lipopolysaccharide.[18] Famotidine and lafutidine have also been shown to significantly decrease the levels of circulating inflammatory mediators. The anti-inflammatory effects of these drugs do not rely on mast cells, rather, they inhibit inflammation through α7 nicotinic acetylcholine receptor signaling - a mechanism integrated within brain-vagal pathways. While roxatidine, famotidine, and lafutidine all exhibit reductions in circulating levels of inflammatory cytokines, cimetidine and ranitidine do not demonstrate anti-inflammatory properties, even at high concentrations.[19,20]

Alleviating Ventricular Remodeling

Cardiomyocyte injury, whether occurring directly or via neurohormonal activation, precipitates eccentric hypertrophy in the surviving cardiomyocytes, fibrosis, progressive dilation of the left ventricle, a transformation in shape from oval to spherical, and often functional mitral regurgitation. These alterations, collectively referred to as left ventricular remodeling, result in increased myocardial oxygen consumption and diminished efficiency of myocardial contraction.[21] In HF scenarios, histamine 2 receptors negatively influence cardiac remodeling by acting on cardiomyocytes, fibroblasts, and even endothelial cells.[22] The hypertrophy observed in cardiomyocytes cultured with histamine and histamine 2 receptor agonists substantiates the role of histamine in cardiac remodeling. Concurrently, it has been demonstrated that famotidine can facilitate recovery from left ventricular hypertrophy and ameliorate ventricular remodeling.[23] One potential mechanism underlying this effect may be associated with elevated levels of ANP. ANP plays several critical roles within the cardiovascular system; it limits cardiomyocyte hypertrophy and apoptosis while reducing cardiac fibrosis and promoting vascular integrity.[23] Cardiac stem cells are vital for maintaining cardiac homeostasis; however, their efficacy is compromised across various heart diseases. Preserving a healthy population of stem cells is essential for preventing adverse heart remodeling. Saheera S et al confirmed through animal experiments that famotidine enhanced both migration and proliferation potential of cardiac stem cells in spontaneously hypertensive rats while preserving stem cell viability. H2RAs restore the functionality of cardiac stem cells by mitigating oxidative stress and thus play a protective role for the myocardium.[24,25]

Reducing Mortality Rate

The use of H2RAs has been shown to reduce mortality in patients with HF. Zhang XS et al utilized the Critical Care Medicine Information Market III database to investigate the association and differences between H2RAs and beta blockers in terms of their impact on mortality in critically ill patients with HF. The findings indicated that H2RAs exhibited a comparable reduction in all-cause mortality as beta blockers, with both classes of drugs possessing similar

pharmacological mechanisms. Furthermore, it was observed that H2RAs and beta blockers may exhibit additive or synergistic effects, thereby enhancing survival rates among critically ill patients with HF.[19,26]

Beneficial Effects on Typical Risk Factors for HF and Prevention of HF

In the context of HF, prioritizing its prevention should be a primary objective within the healthcare system. The risk factors associated with HF are well-documented, with common contributors including hypertension, ischemic heart disease, and diabetes mellitus.[27] Given that HF serves as a pivotal endpoint for virtually all cardiovascular diseases, effective prevention strategies must focus on addressing and managing modifiable risk factors such as high blood pressure and coronary artery disease.[21]

Previous studies have demonstrated that H2RAs exhibit a significant capacity to decrease mean arterial pressure and systemic vascular resistance in critically ill patients. Furthermore, an analysis leveraging the Critical Care Medicine Information Marketplace III database revealed that H2RAs are associated with a reduction in mortality rates among critically ill hypertensive patients. This correlation is particularly pronounced in individuals aged over 60 years with essential hypertension, a body mass index of 25 kg/m^2, and comorbidities such as coronary atherosclerosis, stroke, and acute renal failure.[13] The underlying mechanism for this effect may be attributed to the ability of H2RAs to promote the release of ANP from cardiomyocytes. This process activates ANP receptors located on vascular smooth muscle cells, leading to vasodilation and subsequent reductions in blood pressure.[9]

Recently, studies have demonstrated that acute stress can trigger the activation of myocardial mast cells, leading to the release of histamine. Furthermore, histamine derived from cardiac mast cells has been shown to induce constriction of coronary arteries.[12] Notably, histamine interacts with the H2 receptor rather than the H1 receptor, resulting in a decrease in ANP release. This phenomenon is closely associated with the pathophysiology of cardiac disease linked to activated cardiac mast cells. In this pathological state characterized by mast cell activation and elevated histamine levels, the reduction in ANP release induced by histamine may exacerbate coronary artery dysfunction. Consequently, following administration of H2RAs, increased levels of ANP can lead to dilation of coronary vessels, enhancement of myocardial contractility, and improvement in overall cardiac pumping function.[26]

In a multicenter prospective observational cohort study involving 6378 patients without cardiovascular disease, users of H2RAs exhibited a 62% reduction in the incidence of HF compared to non-users. Over time, morphological changes in the left heart were less pronounced among H2RAs users than their counterparts, indicating that histamine signaling may play a significant role in the pathogenesis of HF and confirming that H2RAs can inhibit or reverse ventricular remodeling.[28] Leary PJ et al conducted an investigation involving 4,122 participants with atherosclerosis but without clinical cardiovascular disease. Their findings revealed that H2RAs usage was associated with reduced right ventricular mass and smaller right ventricular end-diastolic volume. This suggests that H2RAs may have direct clinical implications for cardiopulmonary diseases.[29] In another article, they reported that the rs2241562 minor allele in the H2 histamine receptor gene was exclusively found in Chinese participants and was associated with an elevated risk of HF. Conversely, no associations were observed between H2 histamine receptor single nucleotide polymorphisms and HF in black, Hispanic, or white participants.[30] In summary, H2RAs contribute to the management of vascular and coronary artery dysfunction while inhibiting ventricular remodeling, thereby helping to prevent HF.

Other Considerations to Note

Different H2RAs exhibit varying degrees of efficacy on H2 receptors. Famotidine is recognized as the most potent, followed by roxatidine and ranitidine, which shares an equal potency with nizatidine. Cimetidine ranks last in this hierarchy. Notably, famotidine demonstrates approximately eight times greater potency than ranitidine and forty times greater potency than cimetidine.[22] However, some studies suggest that ranitidine may be superior to famotidine in reducing mortality rates among critically ill patients suffering from HF.[19] Most of these antagonists are inverse agonists with half-lives of 2 to 4 hours. Exposure can cause an increase in H2 receptor density, which is influenced by both the duration of exposure and the administered dose. This upregulation of H2 receptor density leads to elevated basal, ligand-independent activity, ultimately leading to drug tolerance and the manifestation of symptoms associated with histamine overdose or heightened histamine sensitivity.[31] Therefore, when using these drugs over a long period or in large doses, attention should be paid to potential adverse reactions, especially upon discontinuation of the drug.

H2RAs have been shown to effectively prevent gastric and duodenal ulcers, as well as erosive esophagitis, in patients undergoing low-dose aspirin therapy.[32] For patients with no history of upper gastrointestinal bleeding events, H2RAs may serve as an effective and safe alternative to proton pump inhibitors during dual antiplatelet therapy,[8] without compromising the antiplatelet aggregation effect of clopidogrel.[33] However, for patients at risk of gastrointestinal bleeding, proton pump inhibitors are considered superior to H2RAs.[34]

It is also crucial to consider potential interactions between H2RAs and other concurrently administered medications. For instance, H2RAs can bind with captopril, resulting in the formation of charge-transfer complexes that diminish the bioavailability of captopril.[35]

In addition, famotidine has the potential to prolong the QT interval, thereby increasing the risk of arrhythmias, particularly in patients with electrolyte imbalances such as hypomagnesemia and hypocalcemia. Consequently, it may be necessary to monitor both electrocardiographic and electrolyte levels during H2RAs therapy.[36]

Conclusion

H2RAs exhibit therapeutic effects on HF by promoting sodium and water excretion, vasodilation, increasing cardiac output, reducing inflammatory cytokine levels, alleviating ventricular remodeling, and reducing mortality rate. Furthermore, H2RAs may also play a beneficial role in addressing HF-related risk factors, thereby contributing to the prevention of HF. Additional research with larger sample sizes and rigorous methodologies is required to further validate these observations. It is crucial to consider the specific circumstances of the patient, including their medication regimen, complications, and comorbidities, when determining the appropriate use of H2RAs.

Abbreviations

HF, heart failure; H2RAs, histamine H2 receptor antagonists; ANP, atrial natriuretic peptide.

Acknowledgments

Grammar consulting and writing assistance were kindly provided by Ying Liu.

Funding

Funds are not involved in this review.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. *Lancet*. 2019;393(10175):1034–1044. doi:10.1016/S0140-6736(18)31808-7
2. Metra M, Tomasoni D, Adamo M, et al. Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2023;25(6):776–791. doi:10.1002/ejhf.2874
3. Montuoro S, Gentile F, Giannoni A. Neuroimmune cross-talk in heart failure. *Cardiovasc Res*. 2024. doi:10.1093/cvr/cvae236
4. Mody R, Nee Sheth AB, Dash D, et al. Device therapies for heart failure with reduced ejection fraction: a new era. *Front Cardiovasc Med*. 2024;11:1388232. doi:10.3389/fcvm.2024.1388232
5. Ilonze OJ, Forman DE, LeMond L, et al. Beyond Guideline-Directed Medical Therapy: nonpharmacologic Management for Patients With Heart Failure. *JACC Heart Fail*. 2024;2024:1. doi:10.1016/j.jchf.2024.08.018
6. Wernhart S, Papathanasiou M, Rassaf T, Luedike P. The controversial role of beta-blockers in heart failure with preserved ejection fraction. *Pharmacol Ther*. 2023;243:108356. doi:10.1016/j.pharmthera.2023.108356
7. Marti HP, Pavía López AA, Schwartzmann P. Safety and tolerability of β-blockers: importance of cardioselectivity. *Curr Med Res Opin*. 2024;40(sup1):55–62. doi:10.1080/03007995.2024.2317433
8. Chan FK, Kyaw M, Tanigawa T, et al. Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin. *Gastroenterology*. 2017;152(1):105–110.e1. doi:10.1053/j.gastro.2016.09.006
9. Sarzani R, Allevi M, Di Pentima C, Schiavi P, Spannella F, Giulietti F. Role of Cardiac Natriuretic Peptides in Heart Structure and Function. *Int J Mol Sci*. 2022;23(22):14415. doi:10.3390/ijms232214415
10. Rahbar Kouibaran F, Sabatino M, Barozzi C, Diemberger I. Atrial Natriuretic Peptides as a Bridge between Atrial Fibrillation, Heart Failure, and Amyloidosis of the Atria. *Int J Mol Sci*. 2023;24(7):6470. doi:10.3390/ijms24076470

11. Saheera S, Potnuri AG, Guha A, Palaniyandi SS, Thandavarayan RA. Histamine 2 receptors in cardiovascular biology: a friend for the heart. *Drug Discov Today*. 2022;27(1):234–245. doi:10.1016/j.drudis.2021.08.008
12. Li D, Wen JF, Jin JY, Quan HX, Cho KW. Cardiac mast cells regulate myocyte ANP release via histamine H2 receptor in beating rabbit atria. *Regul Pept*. 2009;155(1–3):33–38. doi:10.1016/j.regpep.2009.03.007
13. Pan JM, Guo Y, Jiang FF, et al. Effect of Histamine H2 Receptor Antagonists on All-Cause Mortality in Critically Ill Patients With Essential Hypertension: a Retrospective Cohort Study. *J Clin Pharmacol*. 2024;64(9):1112–1122. doi:10.1002/jcph.2445
14. Tokudome T, Otani K, Mao Y, et al. Endothelial Natriuretic Peptide Receptor 1 Play Crucial Role for Acute and Chronic Blood Pressure Regulation by Atrial Natriuretic Peptide. *Hypertension*. 2022;79(7):1409–1422. doi:10.1161/HYPERTENSIONAHA.121.18114
15. Sugiyama T, Hatanaka Y, Iwatani Y, Jin X, Kawasaki H. Lafutidine facilitates calcitonin gene-related peptide (CGRP) nerve-mediated vasodilation via vanilloid-1 receptors in rat mesenteric resistance arteries. *J Pharmacol Sci*. 2008;106(3):505–511. doi:10.1254/jphs.fp0072259
16. Wróbel-Nowicka K, Wojciechowska C, Jacheć W, Zalewska M, Romuk E. The Role of Oxidative Stress and Inflammatory Parameters in Heart Failure. *Medicina*. 2024;60(5):760. doi:10.3390/medicina60050760
17. Sveklina TS, Shustov SB, Kolyubaeva SN, et al. Inflammatory Biomarkers in Patients With Type 2 Diabetes Mellitus and Heart Failure With Preserved Ejection Faction. *Kardiologiia*. 2024;64(7):40–47. doi:10.18087/cardio.2024.7.n2562
18. Cho EJ, An HJ, Shin JS, et al. Roxatidine suppresses inflammatory responses via inhibition of NF-κB and p38 MAPK activation in LPS-induced RAW 264.7 macrophages. *J Cell Biochem*. 2011;112(12):3648–3659. doi:10.1002/jcb.23294
19. Huang YH, Cai WK, Yin SJ, et al. Histamine H2 receptor antagonist exposure was related to decreased all-cause mortality in critical ill patients with heart failure: a cohort study. *Eur J Prev Cardiol*. 2022;29(14):1854–1865. doi:10.1093/eurjpc/zwac122
20. Zhu L, Guo J, Liu Q, et al. Lafutidine Ameliorates Indomethacin-Induced Small Intestinal Damage in Rats by Modifying the Intestinal Mucosal Barrier, Inflammation, and Microbiota. *Pharmacology*. 2023;108(3):286–300. doi:10.1159/000529879
21. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017;390(10106):1981–1995. doi:10.1016/S0140-6736(17)31071-1
22. Levick SP. Histamine receptors in heart failure. *Heart Fail Rev*. 2022;27(4):1355–1372. doi:10.1007/s10741-021-10166-x
23. Potnuri AG, Allakonda L, Appavoo A, Saheera S, Nair RR. Association of histamine with hypertension-induced cardiac remodeling and reduction of hypertrophy with the histamine-2-receptor antagonist famotidine compared with the beta-blocker metoprolol. *Hypertens Res*. 2018;41(12):1023–1035. doi:10.1038/s41440-018-0109-2
24. Saheera S, Potnuri AG, Nair R. Histamine-2 receptor antagonist famotidine modulates cardiac stem cell characteristics in hypertensive heart disease. *PeerJ*. 2017;5:e3882. doi:10.7717/peerj.3882
25. Kim J, Ogai A, Nakatani S, et al. Impact of blockade of histamine H2 receptors on chronic heart failure revealed by retrospective and prospective randomized studies. *J Am Coll Cardiol*. 2006;48(7):1378–1384. doi:10.1016/j.jacc.2006.05.069
26. Zhang XS, Cai WK, Wang P, et al. Histamine H2 receptor antagonist exhibited comparable all-cause mortality-decreasing effect as β-blockers in critically ill patients with heart failure: a cohort study. *Front Pharmacol*. 2023;14:1273640. doi:10.3389/fphar.2023.1273640
27. Shah UA, Rashid A, Mufti SA, et al. Clinical profile, treatment patterns and one-year outcome of heart failure patients admitted in tertiary care hospital of North India. *J Family Med Prim Care*. 2024;13(8):3225–3230. doi:10.4103/jfmpc.jfmpc_1868_23
28. Leary PJ, Tedford RJ, Bluemke DA, et al. Histamine H2 Receptor Antagonists, Left Ventricular Morphology, and Heart Failure Risk: the Mesa Study. *J Am Coll Cardiol*. 2016;67(13):1544–1552. doi:10.1016/j.jacc.2016.01.045
29. Leary PJ, Barr RG, Bluemke DA, et al. H2 receptor antagonists and right ventricular morphology: the Mesa right ventricle study. *Ann Am Thorac Soc*. 2014;11(9):1379–1386. doi:10.1513/AnnalsATS.201407-344OC
30. Leary PJ, Kronmal RA, Bluemke DA, et al. Histamine H_2 Receptor Polymorphisms, Myocardial Transcripts, and Heart Failure (from the Multi-Ethnic Study of Atherosclerosis and Beta-Blocker Effect on Remodeling and Gene Expression Trial). *Am J Cardiol*. 2018;121(2):256–261. doi:10.1016/j.amjcard.2017.10.016
31. Allen SJ, Chazot PL, Dixon CJ. Can H_2 -receptor upregulation and raised histamine explain an anaphylactoid reaction on cessation of ranitidine in a 19-year-old female? A case report. *Br J Clin Pharmacol*. 2018;84(7):1611–1616. doi:10.1111/bcp.13578
32. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a Phase III, randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9684):119–125. doi:10.1016/S0140-6736(09)61246-0
33. Furtado RHM, Giugliano RP, Strunz CMC, et al. Drug Interaction Between Clopidogrel and Ranitidine or Omeprazole in Stable Coronary Artery Disease: a Double-Blind, Double Dummy, Randomized Study. *Am J Cardiovasc Drugs*. 2016;16(4):275–284. doi:10.1007/s40256-016-0172-5
34. Wei P, Zhuo S, Fu Q, et al. The efficacy and safety of the short-term combination therapy with ticagrelor and PPIs or H2RA in patients with acute STEMI who underwent emergency PCI. *Clin Transl Sci*. 2022;15(2):477–489. doi:10.1111/cts.13165
35. Sultana N, Arayne MS, Quraish R. In vitro interactions of captopril with H2-receptor antagonists. *Pak J Pharm Sci*. 2007;20(2):132–139.
36. Yun J, Hwangbo E, Lee J, et al. Analysis of an ECG record database reveals QT interval prolongation potential of famotidine in a large Korean population. *Cardiovasc Toxicol*. 2015;15(2):197–202. doi:10.1007/s12012-014-9285-8