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Current Research Status and Review of "Non-Cardiovascular Medications" in Heart Failure

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Abstract: Patients with heart failure frequently have multiple comorbidities and often require long-term use of non-cardiovascular medications. Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), glucose-lowering agents, antidepressants, and antibiotics, while improving comorbid conditions, can increase the risks of heart failure deterioration, rehospitalization, and death through hemodynamic interference, electrolyte disturbances, inflammatory responses, and pharmacokinetic interactions. This article systematically reviews the current application status, safety controversies, and monitoring strategies of the above drugs, with an emphasis on analyzing the thrombotic, arrhythmic, and independent cardiovascular and cerebrovascular risks of NSAIDs and PPIs, evaluating the cardiovascular benefits of metformin, SGLT-2 inhibitors, and GLP-1 receptor agonists, and discussing the "dual-heart" model, polypharmacy in the elderly, and pulmonary infection scenarios. Current evidence indicates that non-cardiovascular drugs exert a "double-edged sword" effect on heart failure prognosis. Some drugs require strict restriction of indications and strengthened monitoring, while novel glucose-lowering agents such as SGLT-2 inhibitors possess clear cardiovascular protective effects. In the future, an individualized comprehensive medication monitoring model based on evidence-based medicine and real-world data should be established to balance the benefits of comorbidity treatment against the risk of heart failure deterioration.

Keywords: Heart failure; Non-cardiovascular drugs; Drug interactions; Polypharmacy; Clinical safety

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1. Introduction

1.1. Clinical background and core issues

Patients with heart failure have complex comorbidities and often take non-cardiovascular medications for extended periods. NSAIDs, PPIs, glucose-lowering agents, and psychotropic drugs target comorbidities but may interfere with hemodynamics, induce electrolyte disturbances, exacerbate inflammatory responses, produce pharmacokinetic interactions, weaken the efficacy of standard heart failure therapy, and increase the risks of rehospitalization and death. Current safety assessments lag behind widespread use, risks are underestimated, observational studies are confounded by confounding factors, and randomized controlled

trials have difficulty enrolling patients with severe heart failure due to ethical constraints, leaving gaps in causal evidence. The core issue is to balance comorbidity control with cardiac safety and to establish a risk stratification-based safe medication strategy.

1.2. Research scope and review framework

This article focuses on non-steroidal anti-inflammatory drugs, proton pump inhibitors, glucose-lowering drugs, antidepressants, and antibiotics, integrating the scenarios of polypharmacy in the elderly and pulmonary infection, sorting out the risk mechanisms, evidence-based controversies, and monitoring strategies, and exploring the pathway from single-drug evaluation to comprehensive medication monitoring.

2. Cardiovascular risks of NSAIDs and monitoring

2.1. Risk mechanisms and event characteristics

NSAIDs increase thrombotic risk through pathways including cyclooxygenase inhibition, interference with the coagulation cascade, inhibition of platelet function, or alteration of vascular endothelial homeostasis. Mo Huiping et al. [1] showed that cardiovascular adverse reactions are closely linked to drug and patient factors. The meta-analysis by Yang Zhenzheng [2] showed that NSAIDs increase the risks of upper gastrointestinal complications and cardiovascular disease. Hang Ye et al. [3] pointed out that cardiovascular thrombotic events caused by NSAIDs may be fatal. Long-term use increases the incidence of serious cardiovascular thrombotic events, and indications should be strictly limited in clinical practice.

2.2. Monitoring strategies and domestic–international gaps

Europe and the United States have established corresponding guidelines and expert consensus, which emphasize restricting indications and comprehensively considering drug variety, dose, course of treatment, and patient history. In China, relevant research mostly focuses on risk description and warnings, lacking analysis of independent mechanisms, local big data, and systematic monitoring models. Aodong Tana [4] pointed out that domestic related research is still in its infancy. It is necessary to draw on international experience to promote the formulation of localized guidelines and the conduct of pharmaceutical care.

2.3. Rational drug use and prevention of adverse reactions

Strictly limiting indications is key. Multiple factors, including drug variety, dose, course of treatment, concomitant medications, and patient age, sex, degree of atherosclerosis, and heart failure status, influence the risk of NSAIDs. For young women without a history of hypertension and patients with congestive heart failure, the risk of fatal thrombotic events is relatively higher. In clinical practice, medication assessment models, shortest-course standards, and monitoring models should be established to avoid non-standard use.

3. Cerebrovascular safety controversy of PPIs

3.1. Independent increase in cardiovascular and cerebrovascular risk

The meta-analysis by Liu Fuwei [5], which included 12 cohort studies, showed that PPIs independently increase the risk of stroke (OR = 1.22), myocardial infarction (OR = 1.21), cardiovascular death (OR = 1.83), and all-cause death (OR = 1.94). The analysis by Wang Hong [6], which included 22 studies, further confirmed

that PPIs increase the risk of myocardial infarction (OR = 1.14), stroke (OR = 1.14), heart failure (OR = 1.48), and all-cause death (OR = 1.38), and this risk remained significant in people without prior cardiovascular disease and in myocardial infarction survivors. The independent negative impact of PPIs on heart failure and survival prognosis indicates the need to reassess the benefit–risk ratio of long-term use.

3.2. Arrhythmogenic mechanisms and clinical risks

Fan Weiguo [7] conducted a study based on the MIMIC database and found that pantoprazole and lansoprazole can block cardiac potassium channels, and their increase in QT interval prolongation and ventricular arrhythmia risk does not depend on electrolyte abnormalities. When hypokalemia and hypomagnesemia are present, the combined effect of these two drugs lowers the safety threshold of cardiac repolarization, making torsades de pointes (TdP) more likely. Zhang Guoxing et al. [8] showed that tricyclic antidepressants, citalopram, escitalopram, and venlafaxine can all cause QT interval prolongation and TdP. In clinical practice, vigilance should be maintained regarding the interference of non-cardiovascular drugs with cardiac repolarization under polypharmacy.

3.3. Drug interactions and potentially inappropriate medications in the elderly

When PPIs are used together with clopidogrel, they may compete for CYP2C19, thereby reducing the concentration of the active metabolite of clopidogrel. Luo Shenqiang [9] found that when pantoprazole and omeprazole were used with clopidogrel, there were no statistically significant differences in cardiovascular events or all-cause mortality, but monitoring is still needed. Li Ling [10] pointed out that multi-drug combinations of PPIs may cause multi-system adverse reactions and reduce efficacy. Among polypharmacy in the elderly, proton pump inhibitors (PPIs) are a high-incidence category of potentially inappropriate medications (PIMs). Han Chunxiao [11] showed that the use rate of PPIs in the geriatrics department was 40.9%, of which the proportion with ≥ 5 concomitant medications was 91.6%. Wang Mengge [12] reported that, according to the 2019 Beers Criteria, the incidence of PIMs was 69.7%, of which PPIs accounted for 15.57%; the number of concomitant medications (OR = 2.087), renal failure (OR = 6.514), and Charlson Comorbidity Index (OR = 3.639) were identified as independent risk factors. Screening should be carried out according to the Beers Criteria, and indications and course of treatment should be strictly controlled.

4. Impact of glucose-lowering drugs on cardiovascular outcomes in heart failure

4.1. Safety of traditional and novel glucose-lowering drugs

Metformin has shifted from an early contraindication to a safe and effective drug. Liu Xia et al. [13] showed that metformin has a relatively low risk of heart failure. Yang Zhousheng et al. [14] cited observational studies showing that, compared with sulfonylureas or insulin, metformin alone can reduce the one-year mortality and readmission rates in patients with heart failure, improve survival in patients with low left ventricular ejection fraction (LVEF), and reduce mortality in patients with diabetes and heart failure by approximately 20%. In 2006, the US Food and Drug Administration (FDA) withdrew the contraindication for congestive heart failure, and the European Society of Cardiology (ESC) recommends metformin as first-line treatment for diabetes with heart failure and mild-to-moderate renal impairment.

SGLT-2 inhibitors and GLP-1 receptor agonists have cardiovascular protective effects beyond glucose lowering. The LEADER trial showed that liraglutide reduced major adverse cardiovascular events

(MACE) by 13% and cardiovascular death by 22%; the SUSTAIN-6 trial confirmed that semaglutide reduces cardiovascular events; the EMPA-REG OUTCOME trial showed that empagliflozin reduced heart failure hospitalization by 35% and cardiovascular death by 38%; the CANVAS trial showed that canagliflozin reduced heart failure hospitalization by 33%; and the DECLARE-TIMI 58 trial showed that dapagliflozin has cardiovascular safety and heart failure hospitalization benefits. Saxagliptin increases the risk of heart failure hospitalization, while sitagliptin does not increase cardiovascular risk. The position of guidelines has shifted from focusing on glycemic control to being oriented toward cardiovascular outcomes. SGLT-2 inhibitors and GLP-1 receptor agonists have become the preferred combination therapy for patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.

4.2. Evidence for improving heart failure prognosis and guideline evolution

SGLT-2 inhibitors and GLP-1 receptor agonists have clear evidence for reducing readmission and mortality rates, while traditional drugs and some DPP-4 inhibitors require assessment of heart failure risk. Guideline recommendations are based on cardiovascular outcome trial evidence, with emphasis on individualized treatment. SGLT-2 inhibitors have the potential to simultaneously improve cardiac function and exert antidepressant effects in heart failure with preserved ejection fraction (HFpEF) complicated by depression [15].

4.3. Special application in heart failure complicated by pulmonary infection

The study by Wu Siqi [16] showed that for patients with heart failure complicated by community-acquired pneumonia, the use of SGLT-2 inhibitors was a key protective factor for in-hospital death, with a hazard ratio (HR) of 0.18. This indicates that, under high infection risk, this inhibitor has prognostic protective significance. SGLT-2 inhibitors may improve patient outcomes by modulating inflammatory load. Different glucose-lowering strategies have different effects on inflammatory markers and adverse outcomes, so individualized selection should be made according to infection status.

5. Drug treatment of heart failure complicated by mental and psychological disorders and the dual-heart model

5.1. Interactions between antidepressants and cardiovascular drugs

Antidepressants can improve psychiatric comorbidities, but pharmacokinetic interactions may alter heart failure prognosis. The randomized controlled trial by Li Zhiqiang et al. showed that combining the dual-heart medical model with psychological and behavioral intervention, exercise relaxation, and antidepressants can reduce readmission rates and length of hospital stay and improve cardiac function. Zhang Guoxing et al. proposed that when antidepressants are used together with anticoagulants, antiplatelet drugs, and antiarrhythmic drugs, the risk of bleeding or arrhythmia increases; tricyclic drugs, citalopram, escitalopram, and venlafaxine may cause QT interval prolongation and thereby induce TdP. In clinical practice, refined assessment should be made according to cardiac function status and concomitant medications.

5.2. Efficacy of the dual-heart medical model

After 6 months of follow-up, Li Zhiqiang et al. [17] found that combined intervention reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP), somatization symptoms, and depression and anxiety scores, improved LVEF and 6-minute walking distance, and reduced readmission rates and length of hospital stay. Sheng Chun [18] proposed that screening and intervention for depression can interrupt the vicious cycle of the disease. Liu Xianling et al. [15] pointed out that SGLT-2 inhibitors and angiotensin receptor-neprilysin

inhibitors (ARNI) have the potential to improve cardiac function and exert antidepressant effects in HFpEF complicated by depression. The dual-heart model can improve cardiac function, quality of life, and readmission rates, but attention should be paid to drug interactions and optimization of integrated traditional Chinese and Western medicine approaches.

5.3. Treatment progress in HFpEF complicated by depression

The comorbidity of HFpEF and depression involves immune-inflammatory activation, microvascular endothelial dysfunction, autonomic nervous system dysfunction, and many other aspects. SGLT-2 inhibitors and ARNI, while improving cardiac function prognosis in HFpEF, also have antidepressant effects and may become intervention targets linking cardiac physiology and psychology. In the future, large-sample randomized controlled trials should be conducted to clarify antidepressant mechanisms and applicable populations, and to establish comprehensive drug–psychology–comorbidity strategies.

6. Polypharmacy and pulmonary infection risk in elderly patients with heart failure

6.1. Analysis of potentially inappropriate medications

Wang Mengge [12] reported, according to the 2019 Beers Criteria, that the incidence of PIMs in elderly hospitalized patients with polypharmacy was 69.7%, of which diuretics accounted for 42.11%, PPIs for 15.57%, benzodiazepines for 8.55%, and selective serotonin reuptake inhibitors (SSRIs) for 10.42%. PPIs independently increase the risks of myocardial infarction, stroke, and cardiovascular death, so they should not be used long-term in elderly patients with heart failure without indication. The number of polypharmacy drugs, renal failure, and the Charlson Comorbidity Index are positively correlated with PIMs. The shortest course, strict indications, and pharmaceutical care should be followed.

6.2. Risk factors for pulmonary infection and antibiotic use

Li Dandan [19] found that age 80 years and older, smoking behavior, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), antibiotic misuse, and long-term bedridden status are independent risk factors for pulmonary infection in elderly patients with heart failure. Li Yanning [20] confirmed through research that age, antibiotic use, smoking history, presence of chronic diseases, left ventricular ejection fraction (LVEF), and increased length of hospital stay all increase infection risk. Wang Xiaoya et al. [21] pointed out that invasive procedures and prolonged antibiotic use increase the risks of drug resistance and secondary infection. Wu Siqi [16] found that the use of extended-spectrum antibiotics (HR = 5.28) and invasive procedures (HR = 2.94) were independent risk factors for in-hospital death or readmission. Precise antibacterial treatment should be based on etiology to reduce antibiotic misuse.

6.3. Etiological characteristics and treatment strategies

Zeng Xiaoman et al. [22] reported that the detection rate of Gram-negative bacteria in patients with heart failure complicated by pulmonary infection was 73.19%, mainly Acinetobacter baumannii, Klebsiella pneumoniae, and Pseudomonas aeruginosa, and the resistance rate of these bacteria to quinolones exceeded 50%, with some exceeding 70%. Wu Siqi [16] reported that among bacterial infections, Gram-negative bacteria accounted for 56.1%, with Pseudomonas aeruginosa and Klebsiella pneumoniae being the two most common,

and the use rate of extended-spectrum antibiotics was 60.9%. C-reactive protein (CRP) is a key marker for prognosis assessment: Wang Xiaoya et al. [21] found that high-sensitivity C-reactive protein (hs-CRP) was positively correlated with infection severity, and Wu Siqi [16] showed that the 30-day and 1-year risks of all-cause death or readmission were significantly increased in the group with CRP ≥ 61.30 mg/L, with a composite endpoint HR of 2.50. CRP should be incorporated into routine monitoring and risk stratification.

7. Conclusion and prospects

7.1. Risk–benefit balance strategy

Non-cardiovascular drugs have a "double-edged sword" effect on heart failure prognosis: drugs such as NSAIDs, PPIs, and some antidepressants can interfere with hemodynamics, electrolytes, and drug metabolism, thereby increasing the risk of heart failure deterioration, while novel glucose-lowering drugs such as SGLT-2 inhibitors have cardiovascular protective effects. At present, there is a lack of interdisciplinary medication risk assessment models targeting the special pathological state of heart failure, and the superimposed risks of polypharmacy are often underestimated. A comprehensive medication monitoring model for the entire disease course should be established, using real-world big data and artificial intelligence to quantify net clinical benefits dynamically.

7.2. Future research directions

Research should shift from single-drug safety evaluation to systematic and comprehensive analysis of the drug–disease–drug interaction network in the context of polypharmacy. A comprehensive medication monitoring model should be established, integrating genomics, metabolomics, and clinical phenotypes, and an intelligent decision support system that can dynamically predict individualized risks and optimize combination therapy should be developed, promoting the transformation of heart failure management toward precision, systematization, and full-cycle smart healthcare.

7.3. Individualized medication decision model

Most existing evidence presents an "atomized" evaluation approach that ignores the nonlinear cascade effects among drugs, diseases, and drugs in elderly patients. In future related research, real-world big data and artificial intelligence technology should be used to quantify cumulative risk and predict interaction effects, incorporating non-cardiovascular drugs into the closed-loop monitoring model of the entire heart failure disease course, thereby achieving collaborative optimization of comorbidity treatment and heart failure prognosis.

Disclosure statement

The author declares no conflict of interest.

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