General Aspects of Pharmacological Treatment of Heart Failure: A Literature Review

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Abstract

In today's world, heart failure poses a global health threat, affecting approximately 64 million people. This progressive condition is characterized by a low long-term survivability: the probability of survival after 1, 2, 5 and 10 years is 87%, 73%, 57% and 35%, respectively. Such statistics highlight the urgent need for therapeutic strategies to improve the prognosis and quality of life of the patient.

The contemporary treatment and management of heart failure is pharmacological, involving the use of a multi-drug regimen, which usually includes five different classes of drugs. These are: 1) diuretics, which are mainly used for reducing/resolving fluid overload; 2) mineralocorticoid receptor antagonists, which block the effects of aldosterone on the heart and blood vessels; 3) Sodium-glucose cotransporter 2 inhibitors, a new class that has shown remarkable benefits in heart failure hospitalizations and cardiovascular mortality; 4) Beta-blockers, which are crucial for modulating the activity of the sympathetic nervous system; and 5) Renin-angiotensin-aldosterone system inhibitors, which include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or the newer angiotensin receptor-neprilysin inhibitors, which play a role in modulating neurohormonal activation. The mechanisms of action, characteristic factors, correct traction methods, and currently available medical trials of these 5 classes of drugs were collected and studied. Ultimately, the correct utilization and use of these pharmacological agents is not only beneficial but necessary for effectively managing heart failure and offering patients a guideline-mediated treatment plan, which is necessary for improving their daily lives and raising long-term survivability.

Keywords: Chronic heart failure; Reduced ejection fraction; diuretics; mineralocorticoid receptor antagonists; Sodium-glucose cotransporter 2 inhibitor; Beta-blockers; Renin-angiotensin-aldosterone system inhibitors; Angiotensin II receptor blockers; Angiotensin receptor-neprilysin inhibitors.

გულის უკმარისობით ფარმაკოლოგიური მკურნალობის ზოგადი ასპექტები: ლიტერატურის მიმოხილვა

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დღევანდელ მსოფლიოში გულის უკმარისობა გლობალურ საფრთხეს წარმოადგენს ჯანმრთელობისთვის, რომელიც დაახლოებით 64 მილიონ ადამიანს აზიანებს. ეს პროგრესირებადი მდგომარეობა ხასიათდება დაბალი გრძელვადიანი გადარჩენის დონით: 1, 2, 5 და 10 წლის შემდეგ გადარჩენის ალბათობა შესაბამისად 87%, 73%, 57% და 35%-ია. ასეთი სტატისტიკა ხაზს უსვამს პაციენტის პროგნოზისა და ცხოვრების ხარისხის გასაუმჯობესებლად თერაპიული სტრატეგიების სასწრაფო საჭიროებას.

გულის უკმარისობის თანამედროვე მკურნალობა და მართვა ფარმაკოლოგიურია, რაც გულისხმობს მრავალწამლის რეჟიმის გამოყენებას, რომელიც ჩვეულებრივ მოიცავს წამლების ხუთ სხვადასხვა კლასს. ესენია: 1) შარდმდენები, რომლებიც ძირითადად გამოიყენება სითხით გადატვირთვის შესამცირებლად/მოგვარებისთვის; 2) მინერალოკორტიკოიდური რეცეპტორების ანტაგონისტები, რომლებიც ბლოკავენ ალდოსტერონის ეფექტს გულსა და სისხლძარღვებზე; 3) ნატრიუმ-გლუკოზის კოტრანსპორტერ 2 ინჰიბიტორები, ახალი კლასი, რომელმაც აჩვენა შესანიშნავი სარგებელი გულის უკმარისობით გამოწვეული ჰოსპიტალიზაციისა და გულ-სისხლძარღვთა სიკვდილიანობის დროს; 4) ბეტა-ბლოკატორები, რომლებიც გადამწყვეტია სიმპათიკური ნერვული სისტემის აქტივობის მოდულირებისთვის; და 5) რენინ-ანგიოტენზინ-ალდოსტერონის სისტემის ინჰიბიტორები, რომლებიც

მოიცავს ანგიოტენზინ-გარდამქმნელი ფერმენტის ინჰიბიტორებს, ანგიოტენზინ II რეცეპტორების ბლოკატორებს ან უფრო ახალ ანგიოტენზინ რეცეპტორ-ნეპრილიზინის ინჰიბიტორებს, რომლებიც როლს ასრულებენ ნეიროჰორმონალური აქტივაციის მოდულაციაში. შეგროვდა და შესწავლილი იქნა ამ 5 კლასის პრეპარატის მოქმედების მექანიზმები, დამახასიათებელი ფაქტორები, სწორი ტრაქციის მეთოდები და ამჟამად ხელმისაწვდომი სამედიცინო კვლევები. საბოლოო ჯამში, ამ ფარმაკოლოგიური აგენტების სწორი გამოყენება და გამოყენება არა მხოლოდ სასარგებლოა, არამედ აუცილებელია გულის უკმარისობის ეფექტური მართვისა და პაციენტებისთვის სახელმძღვანელო პრინციპებით განპირობებული მკურნალობის გეგმის შეთავაზებისთვის, რაც აუცილებელია მათი ყოველდღიური ცხოვრების გასაუმჯობესებლად და გრძელვადიანი გადარჩენის შესაძლებლობის ასამაღლებლად.

საკვანძო სიტყვები: ქრონიკული გულის უკმარისობა; შემცირებული განდევნის ფრაქცია; შარდმდენები; მინერალოკორტიკოიდური რეცეპტორების ანტაგონისტები; ნატრიუმის-გლუკოზის კოტრანსპორტერ 2 ინჰიბიტორი; ბეტა-ბლოკატორები; რენინ-ანგიოტენზინ-ალდოსტერონის სისტემის ინჰიბიტორები; ანგიოტენზინ II რეცეპტორების ბლოკატორები; ანგიოტენზინ რეცეპტორ-ნეპრილიზინის ინჰიბიტორები.

Heart failure is a clinical syndrome characterized by typical symptoms (such as dyspnea, ankle swelling, and fatigue) accompanied by specific signs (elevated jugular venous pressure, pulmonary rales, and peripheral edema). It is caused by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during exertion.[1] The 2013 guidelines of the American College of Cardiology Foundation / American Heart Association (ACCF/AHA) define two types of heart failure: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Preserved ejection fraction (EF) is defined as 50% or higher, while reduced EF is defined as 40% or lower. Patients with an EF between more than 40% but less than 50% represent an intermediate group whose treatment is similar to that for HFpEF.[2]

Patients with heart failure may be assigned different classes and/or stages of heart failure. The New York Heart Association (NYHA) classification defines four classes:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of heart failure.
- Class II: No symptoms at rest, but ordinary physical activity results in symptoms of heart failure.

•Class III: No symptoms at rest, but less than ordinary physical activity causes symptoms of heart failure.

•Class IV: Symptoms of heart failure are present even at rest.

The ACCF/AHA also defines four stages of heart failure:

- Stage A: High risk for developing heart failure, but without structural heart disease or symptoms of heart failure.
- Stage B: Structural heart disease, but without signs or symptoms of heart failure.
- Stage C: Structural heart disease with prior or current symptoms of heart failure.
- Stage D: Refractory heart failure syndrome requiring specialized interventions.[3]

Currently**,** more than 64 million people worldwide have heart failure.[4] [5] Based on echocardiographic screening, the prevalence of any heart failure in developed countries is 11.8%**.**[6] Studies have also shown that the lifetime risk of developing heart failure (between the ages of 45 and 95) is: 30–42% in White men; 20–29% in Black men; 23–39% in White women; 24–46% in Black women.[7] The prognosis worsens with disease progression. Large-scale studies (analyzing all types of heart failure, with 1.5 million patients) have shown that survival rates for patients with heart failure at 1, 2, 5, and 10 years are 87%, 73%, 57%, and 35%**,** respectively. These findings underscore the importance of timely and appropriate therapeutic strategies.[8] Elevated concentrations of inflammatory biomarkers used for prophylaxis are commonly observed in all forms of heart failure and are associated with disease severity and mortality. [9] [10]

The role of sympathetic activation in the progression of heart failure is well known (see Figure 1).[11]

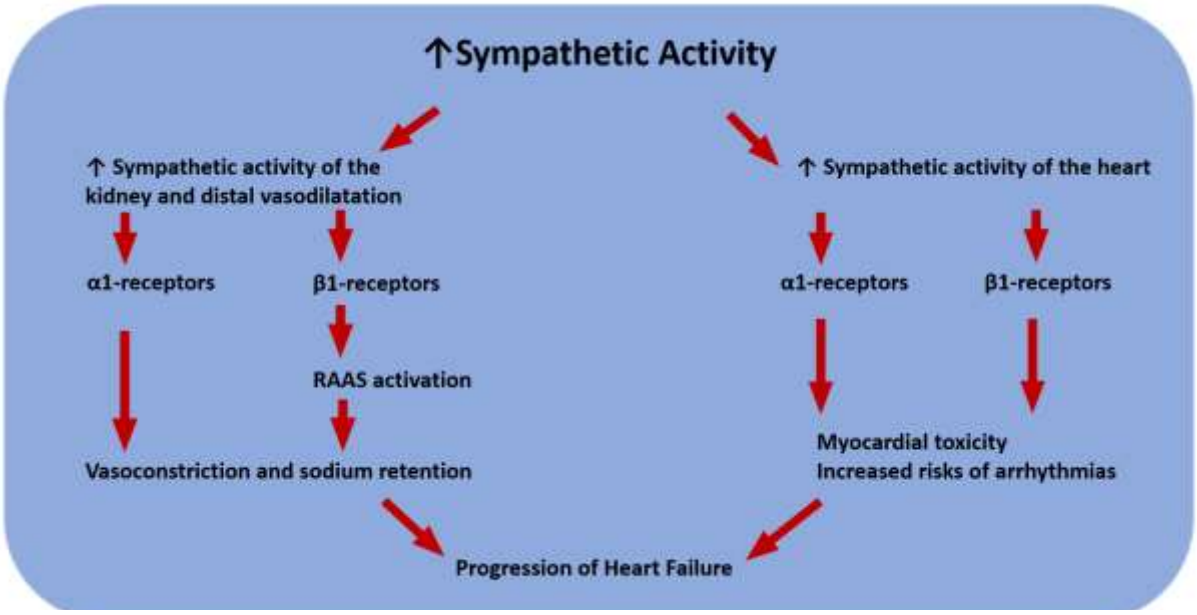

Figure 1 A simple diagram of the progression of heart failure through increased sympathetic activity of the heart

Congestive heart failure is one of the most common complications of ischemic heart disease. Conversely, after hypertension, ischemic heart disease is the leading cause of developing congestive heart failure. Among patients with congestive heart failure, ischemic heart disease is present in 46% of men and 26% of women. In ischemic heart disease, impairment of one of the heart's most vital functions, the blood-pumping ability, is common. This dysfunction can result from various conditions and abnormalities, including myocardial infarction, acute transient ischemia, right ventricular dysfunction, cardiogenic shock, acute mitral regurgitation, ventricular septal rupture, ventricular wall rupture, ischemic cardiomyopathy, ventricular aneurysm, iatrogenic interventions, and, often, cases of pseudofailure of the heart. To this day, the etiology and pathogenesis of congestive heart failure are not fully understood. This creates significant challenges in both diagnosis and treatment. Advances in the study of myocardial mechanics are gradually revealing the highly complex system behind cardiac contractility. In order to evaluate myocardial contractile function, it is essential to consider all factors that influence myocardial contractility. As long as cardiac physiology — and thus pathophysiology — remains incompletely understood, a comprehensive evaluation of contractile function remains beyond reach.

Today, it is also believed that the mechanism of myocardial relaxation is no less complex than that of contraction. Due to the intricacies of this relaxation process, numerous indices have been proposed to evaluate the diastolic function of the myocardium. However, none of them provides a complete picture of all aspects of diastolic function. The development of new, more informative indicators remains an important goal for the future. Based on the above, the study of myocardial contraction and relaxation mechanisms, as well as the evaluation of systolic and diastolic functions, is a highly relevant issue, as these factors play a crucial role in selecting proper treatment strategies and assessing the effects of drugs on the heart's function as a pump.

Currently, the management and treatment of heart failure are significantly limited and primarily involve the use of medications:

1. Diuretics
2. Mineralocorticoid receptor antagonists
3. Sodium-glucose co-transporter 2 (SGLT2) inhibitors
4. Beta-blockers
5. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or angiotensin receptor–neprilysin inhibitors (ARNIs)

Modern medicine tells us that appropriate titration and dosing of these five drug classes can reduce cardiac preload and filling pressures — thereby alleviating the symptoms of heart failure, stabilizing the patient, improving quality of life, and reducing mortality rates.

Group 1 – Diuretics

In congestive heart failure, the primary function of diuretics is to maintain the patient's euvolemic status, or in cases of exacerbation, to eliminate excess fluid from the body in hypervolemic patients.

Assessment of a patient's hypervolemic status can be done through physical examination and laboratory/instrumental studies.

During physical examination: In left-sided heart failure, findings may include dyspnea at rest or with exertion, orthopnea, third heart sound (S3), and rales on auscultation. In right-sided heart failure, one may observe bilateral lower extremity edema, a positive hepatojugular reflux, and dilated jugular veins (diameter >8 cm). Among instrumental tests, ultrasound provides the most rapid and reliable data: In left-sided heart failure, signs include elevated left ventricular filling pressure, demonstrated by lateral E/e' >12, and diastolic dysfunction, shown by mitral inflow E-wave velocity >50 cm/s. In right-sided heart failure, we can assess inferior vena cava (IVC) diameter and the absence of >50% collapse with inspiration, which indicates volume overload. Diuretics used in heart failure can be divided into two main groups: Loop diuretics (acting on the loop of Henle). [12]

Thiazide diuretics. Loop diuretics are the cornerstone of pharmacological therapy for heart failure. The most widely used loop diuretics are: Furosemide; Torasemide; Bumetanide.

Currently, furosemide is the most commonly used loop diuretic in clinical practice. These drugs act by inhibiting the Na^+-K^+-$2Cl^-$ cotransporter in the loop of Henle, leading to increased natriuresis.[13] These three medications differ in bioavailability, which necessitates dose conversion when switching between them (see table 1).[14] [15]

Drug	Oral Dose	Intravenous Dose
Furosemide	40 mg	20 mg
Torasemide	10-20 mg	10-20 mg
Bumetanide	1 mg	1 mg

Table 1 Diuretic conversion table

A study called TORIC, which included 1377 patients, found that the use of torasemide was associated with lower mortality compared to furosemide (2.2% vs. 4.5%, respectively). A greater proportion of patients treated with torasemide showed improvement in functional class (NYHA class), and torasemide was also associated with a lower incidence of hypokalemia (pathologically low serum potassium levels).[16]

Another study involving 16277 patients showed that bumetanide was associated with a higher mortality rate compared to torasemide (19.7% vs. 16.0%, respectively).[17]

A meta-analysis of 18 randomized controlled trials involving 1598 patients with heart failure compared torasemide and furosemide. Torasemide (20 mg) resulted in greater urine output compared to furosemide (40 mg). While overall mortality, edema, weight loss, heart rate, and blood pressure did not differ significantly between the two diuretics, oral torasemide was associated with shorter hospital stays and improvements in ejection fraction. These findings suggest that torasemide may offer benefits in the management of heart failure, although further research is needed.[18]

Currently, there are two strategies for the administration of loop diuretics: intermittent bolus and continuous infusion. In the treatment of patients with acute decompensated heart failure, choosing the correct method of drug administration is essential. According to current guidelines, the most optimal method is to start with an initial bolus at double the patient's usual dose, followed by a continuous infusion. After a single bolus dose, as the drug concentration in the body decreases, sympathetic stimulation increases, leading to enhanced sodium retention. Therefore, continuous infusion following the bolus is preferred.[19] [20] During diuretic therapy, it is essential to protect the patient from acute kidney injury, which can be monitored by frequent laboratory testing of glomerular filtration rate (GFR) (estimated by serum creatinine) and blood urea nitrogen (BUN) levels. An increased BUN/creatinine ratio (>20:1) indicates a pre-renal cause of injury. If kidney damage is suspected, a reduction in diuretic dose is required.[21] When there is a sharp reduction in extracellular fluid volume, the renin–angiotensin–aldosterone system (RAAS) is activated, sympathetic stimulation increases, and hypertrophy of the distal nephron begins. As a result, the body's responsiveness to diuretics decreases. If these processes are prolonged, they may lead to the development of diuretic resistance. [22] [23] This phenomenon is seen as a reduction in urinary sodium concentration. The development of diuretic resistance is associated with frequent hospitalizations and a higher risk of mortality. In such patients, it may become necessary to: Increase the dose of the medication; Switch to a pharmacokinetically stronger diuretic (e.g., replacing furosemide with torasemide); Add a thiazide diuretic; Or add an aldosterone antagonist.[24]

Thiazide diuretics are significantly weaker than loop diuretics. They act by blocking sodium reabsorption through inhibition of the Na-Cl cotransporter. Thiazides are primarily used in combination with loop diuretics in patients with diuretic resistance.[25] Use of thiazide diuretics increases potassium loss in the urine, making frequent monitoring of electrolytes essential.[26]

Group 2 – Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid receptor antagonists (MRAs) are significantly weaker diuretics compared to loop diuretics and thiazide diuretics. Their main use in chronic heart failure is to inhibit aldosterone receptors.[27] Elevated levels of aldosterone stimulate myocardial fibrosis, which in

turn accelerates the progression of heart failure.[28] Currently, the most widely used MRAs are spironolactone and eplerenone. In patients with heart failure, the main effect of these drugs is not enhanced diuresis, but rather the blockade of the aldosterone system.

A randomized, prospective study — RALES, which included 1663 patients with reduced ejection fraction (≤35%) and high NYHA class (III or IV) — demonstrated that spironolactone reduced sudden cardiac death compared to placebo (10% vs. 13.1%, p=0.02), and reduced heart failure–related mortality (15.5% vs. 22.5%, p<0.001), both in patients with normal and reduced glomerular filtration rate (GFR). The RALES study established spironolactone as a key component of therapy in patients with severe heart failure and reduced ejection fraction, and its findings led to the inclusion of aldosterone antagonists in heart failure treatment guidelines, resulting in significant improvement in patient outcomes.[29]

The TOPCAT study, which included 3445 patients with preserved or mid-range ejection fraction (EF ≥45%), confirmed that spironolactone reduced mortality risk and hospitalization frequency over a long-term period (3.3 years).[30]

The EPHESUS trial, involving 6632 patients, demonstrated positive outcomes with eplerenone in patients with left ventricular systolic dysfunction and/or myocardial infarction. Elevated aldosterone levels in these patients were associated with more frequent heart failure events, and eplerenone was shown to reduce these aldosterone-related events.[31]

The EMPHASIS-HF study, with 2737 patients with significantly reduced EF (≤35%), demonstrated a 37% reduction in cardiovascular death or first hospitalization due to heart failure, and a 24% reduction in all-cause mortality. It also showed a 42% reduction in the incidence of new-onset atrial fibrillation. These findings led to a broader recommendation for the use of MRAs in heart failure treatment guidelines.[32]

Another beneficial effect of MRAs is seen when used in combination with other diuretics - they help reduce the risk of hypokalemia.[33]

It is important to underline the side effects from these medications. Because spironolactone is a non-selective mineralocorticoid receptor blocker, compared to eplerenone, it is more likely to cause hormonal side effects, such as gynecomastia.[34]

Group 3 - Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) is located in the proximal tubule of the nephron and is responsible for reabsorbing filtered glucose back into the body. Since this cotransporter lacks negative feedback mechanisms, an increase in secreted glucose concentration leads to a proportionate increase in reabsorbed glucose, without reaching a plateau.[35] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially developed to reduce the reabsorbed glucose concentration in patients with type 2 diabetes. However, clinical trials have revealed their

significant positive influence in managing patients with heart failure (HF). The primary active effect of SGLT2 inhibitors in heart failure patients is natriuresis and the resulting diuresis. Unlike loop and thiazide diuretics, SGLT2i do not activate the sympathetic nervous system, counteract the development of hyperglycemia and hyperuricemia, and reduce glomerular filtration and intraglomerular pressure. It is hypothesized that the elevated concentrations of sodium and chloride delivered to the macula densa by this mechanism contribute to the inhibition of the renin-angiotensin-aldosterone system (RAAS), leading to reduced aldosterone levels and decreased sympathetic impulses.[36]

The EMPA-REG OUTCOME trial, involving 7020 patients, demonstrated that empagliflozin significantly reduced the risk of hospitalizations by 35% and the risk of major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke) by 14%.[37]

The CANVAS program, which studied 15494 patients, showed similar results, with a 33% reduction in the frequency of hospitalizations and a 27% reduction in albuminuria.[38]

The DECLARE-TIMI 58 trial, involving 17160 patients receiving dapagliflozin, observed a 16% reduction in the risk of MACE in the cohort of patients with a history of myocardial infarction. A significant reduction in hospitalization rates and cardiovascular mortality risk was also noted.[39]

It's also important to highlight the EMPEROR-Reduced and DAPA-HF trials, which enrolled 3730 and 4744 patients, respectively. In both studies, patients had reduced ejection fraction (EF $\leq$ 40%) and elevated NT-proBNP levels (notably, the minimum NT-proBNP level for inclusion in EMPEROR-Reduced was higher than in DAPA-HF, indicating that EMPEROR-Reduced included patients with more severe heart failure). DAPA-HF showed a statistically significant reduction in all-cause mortality, while EMPEROR-Reduced showed a numerical, but not statistically significant, reduction in all-cause and cardiovascular mortality. However, a meta-analysis of both trials confirmed a significant reduction in both all-cause and cardiovascular mortality in heart failure with reduced ejection fraction (HFrEF) with SGLT2 inhibition. Essentially, both DAPA-HF and EMPEROR-Reduced provided robust evidence that SGLT2 inhibitors (dapagliflozin and empagliflozin, respectively) are highly effective in reducing heart failure-related hospitalizations and improving cardiovascular outcomes in patients with cardiovascular disease, regardless of their diabetes status. The minor differences in patient populations and the specific statistical significance of individual endpoints should be considered within the context of the overall consistent and significant benefits demonstrated by this class of drugs.[40] [41] [42]

Group 4 - Beta-Blockers

Beta-blockers are a class of medications primarily used to treat a wide range of cardiovascular conditions, including hypertension, angina, heart failure, and arrhythmias. They exert their therapeutic effects by blocking the action of adrenaline and noradrenaline on beta-adrenergic

receptors, predominantly in the heart and blood vessels. This action leads to a reduction in heart rate, myocardial contractility, and blood pressure, thereby decreasing the heart's workload and oxygen demand.[43] In clinical practice, due to various patient comorbidities or the emergence of adverse drug effects, it's often impossible to titrate medications to their maximum recommended dose for all patients. Only 22% of patients reach the recommended dose of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs), and a mere 12% achieve the optimal dose of beta-blockers.[44] The positive effects of beta-blockers in heart failure patients manifest through a reduction in sympathetic activity, catecholamine levels, and pulse rate. Beta-blockers also contribute to left ventricular remodeling in younger/middle-aged hypertensive patients and mitigate the inflammatory state present in heart failure.[45] In practice, beta-blockers are most frequently used in the management and treatment of heart failure with reduced ejection fraction (HFrEF). For stable heart failure, it's recommended to initiate beta-blockers as early as possible and titrate them to a high dose.[46] Studies have shown that titration to a high dose of beta-blockers is associated with longer survival in patients with HFrEF.[47] The most widely used beta-blockers in heart failure are bisoprolol (a competitive inhibitor of beta1-adrenergic receptors), carvedilol (a competitive inhibitor of beta1, beta2, and alpha1 adrenergic receptors), and metoprolol (a competitive inhibitor of beta1-adrenergic receptors). Proper dosing and titration are crucial when prescribing beta-blockers.[48] Evidence-based medicine also underlines the role of beta-blockers in cardiac remodeling; they reduce left ventricular dilation and the risk of developing a spherical shape, decrease mitral valve regurgitation, and improve ejection fraction.[49] [50]

Studies have also shown that correct dosing remains a significant challenge today; among 83605 studied HFrEF patients, 81.4% received beta-blockers, but only 49% of those received ≥50% of the guideline-recommended target dose. [51]

A study involving 72336 patients compared mortality rates between heart failure patients on high versus low doses of beta-blockers. The study demonstrated that high doses of beta-blockers were associated with better survival. Alongside titrating to high doses of beta-blockers, it's also important to remember that abrupt discontinuation of the medication can lead to dangerous side effects (hypertension, tachycardia, myocardial infarction). If dose reduction is necessary, gradual titration to a lower dose is required. [52]

A study spanning over four years, involving 11558 patients, showed that in the presence of comorbidities (e.g., chronic obstructive pulmonary disease), bisoprolol is associated with more positive outcomes. [53]

Studies have also highlighted bisoprolol's ability to protect against myocardial damage.[54] Studies have also shown that bisoprolol has a stronger anti-adrenergic effect than metoprolol and

carvedilol, which clinically translates into improvements in important parameters such as the 6-minute walk test, quality of life, ejection fraction, NYHA class, and blood NT-proBNP levels.[55] [56] Potential side effects of beta-blocker use include bradycardia, hypotension, dizziness, and depression. Consequently, it is not possible to administer beta-blockers at guideline-recommended doses to patients with high NYHA class (NYHA IV), conduction problems/block, or hypotension. Bisoprolol is also not characterized by metabolic disturbances.[57] Therefore, bisoprolol is often preferred among beta-blockers in the treatment of heart failure. Bisoprolol exhibits significantly higher selectivity for beta1 receptors than other beta-blockers. This characteristic makes it better tolerated in patient groups with chronic obstructive pulmonary disease (COPD) and peripheral vascular disease.[58] [59] The majority of bisoprolol (90%) is absorbed via the enteric tract. Approximately 30% binds to plasma proteins. 50% undergoes metabolism in the liver, and 50% is excreted by the kidneys. The half-life of bisoprolol is 10-11 hours in patients with normal glomerular filtration rate and up to 17±5 hours in patients with impaired renal function.[60]

The CIBIS and CIBIS-II trials played a significant role in revealing bisoprolol's potential. In the CIBIS trial, patients (n=641) received no more than 5 mg of bisoprolol daily. While mortality did not significantly change as a result of this study, it demonstrated the tolerability of bisoprolol in heart failure patients without severe side effects. In the CIBIS-II trial, patients (n=2647) received bisoprolol at a higher dose (all patients were titrated to 10 mg daily). Researchers observed a stark difference in mortality between the study and placebo groups – an annual mortality of 8.8% in the study group versus 13.2% in the placebo group, with the incidence of sudden death being 45% higher in the placebo group compared to the study group. The frequency of hospitalizations also decreased by 32%. The results of the CIBIS-II trial were so positive that the study was prematurely halted to share the findings. These two studies highlighted the benefits of high-dose titration and contributed to the popularization of beta-blockers in heart failure patients.[61] [62] The CIBIS study underscored bisoprolol's impact on pulse rate changes as a predictor of survival; the more pronounced the pulse rate change with bisoprolol administration, the more vital the patient.[63] The CIBIS-II study, however, demonstrated that increased survival was an independent phenomenon from pulse rate changes and that this positive factor stemmed from bisoprolol's activity, not directly from pulse rate changes.[64]

Other studies have also highlighted the effect of beta-blockers on survival. The OPTIMIZE-HF program was established, which helped popularize beta-blockers. The 17241 patients registered in it were divided into two cohorts – patients with systolic dysfunction and those with preserved systolic function. Analysis of these cohorts again underscored the effectiveness of beta-blockers in increasing lifespan in the context of reduced ejection fraction. The study also highlighted the lesser effectiveness of beta-blockers in cases of preserved systolic function.[65]

Given the positive effects on lifespan and quality of life, it is easy to see why the inability to titrate beta-blockers to high doses remains a major problem in managing heart failure patients.[66] [67] [68]

The European Society of Cardiology Heart Failure Pilot Survey showed that only a small proportion of studied patients were able to reach the target dose of beta-blockers: carvedilol - 37%, bisoprolol - 21%, metoprolol - 37%.[69] In the CIBIS-ELD trial, 25% of participating patients were able to reach and maintain the guideline-recommended target dose of bisoprolol or carvedilol. The study involved 41 centers and lasted 12 weeks.[70] In a study involving 12493 patients, only 17.8% achieved the recommended dose of beta-blockers.[71]

One reason for the inability to titrate medications to target doses is the more frequent and severe side effects that occur with higher doses of the medication. The second reason for the inability to titrate medications to higher doses is the presence of numerous other diseases in heart failure patients that exacerbate their condition and complicate the treatment process (Figure 2).[72]

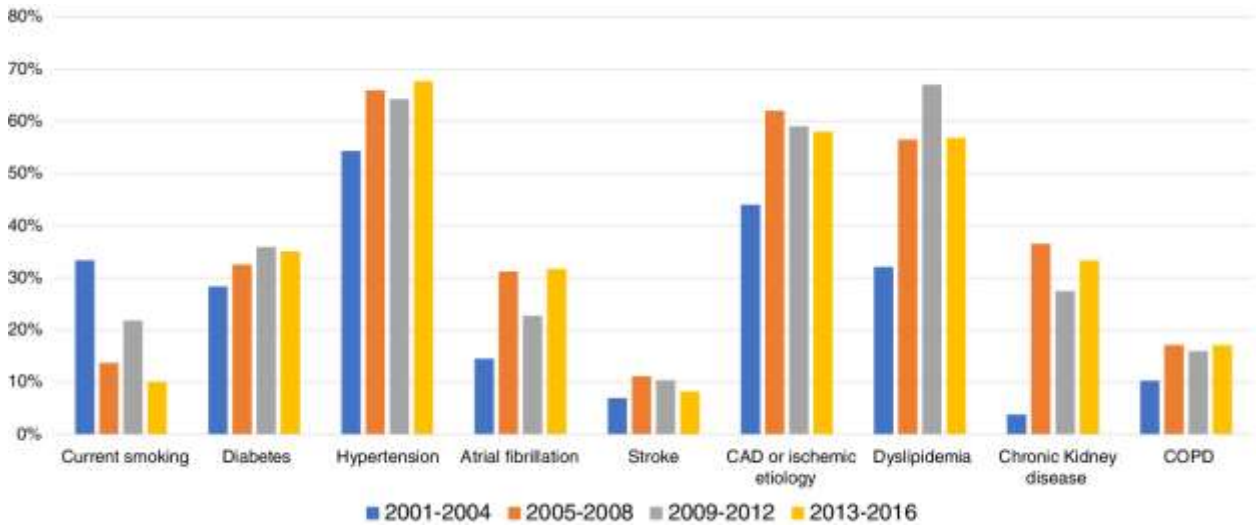

Figure 2 Trends in major comorbidities across all heart failure clinical trials. Smoking prevalence decreased over time, while the prevalence of cardiometabolic comorbidities increased. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

Group 5 - Angiotensin Receptor Blockers

In the context of heart failure, the renin-angiotensin-aldosterone system (RAAS) plays a central role in the development of its pathogenesis. An increase in angiotensin II levels contributes to many complications of heart failure, including hypertrophy, left ventricular dysfunction, myocardial infarction, and congestive heart failure.[73] Angiotensin receptors can be divided into two main types: AT1 receptors and AT2 receptors. AT1 receptors are primarily located in blood vessels and myocardial nerve endings, while AT2 receptors are found in the myocardial interstitial space. Angiotensin Receptor Blockers (ARBs) work by blocking AT1 receptors, making angiotensin II more readily available for AT2 receptors (see Figure 3).[74]

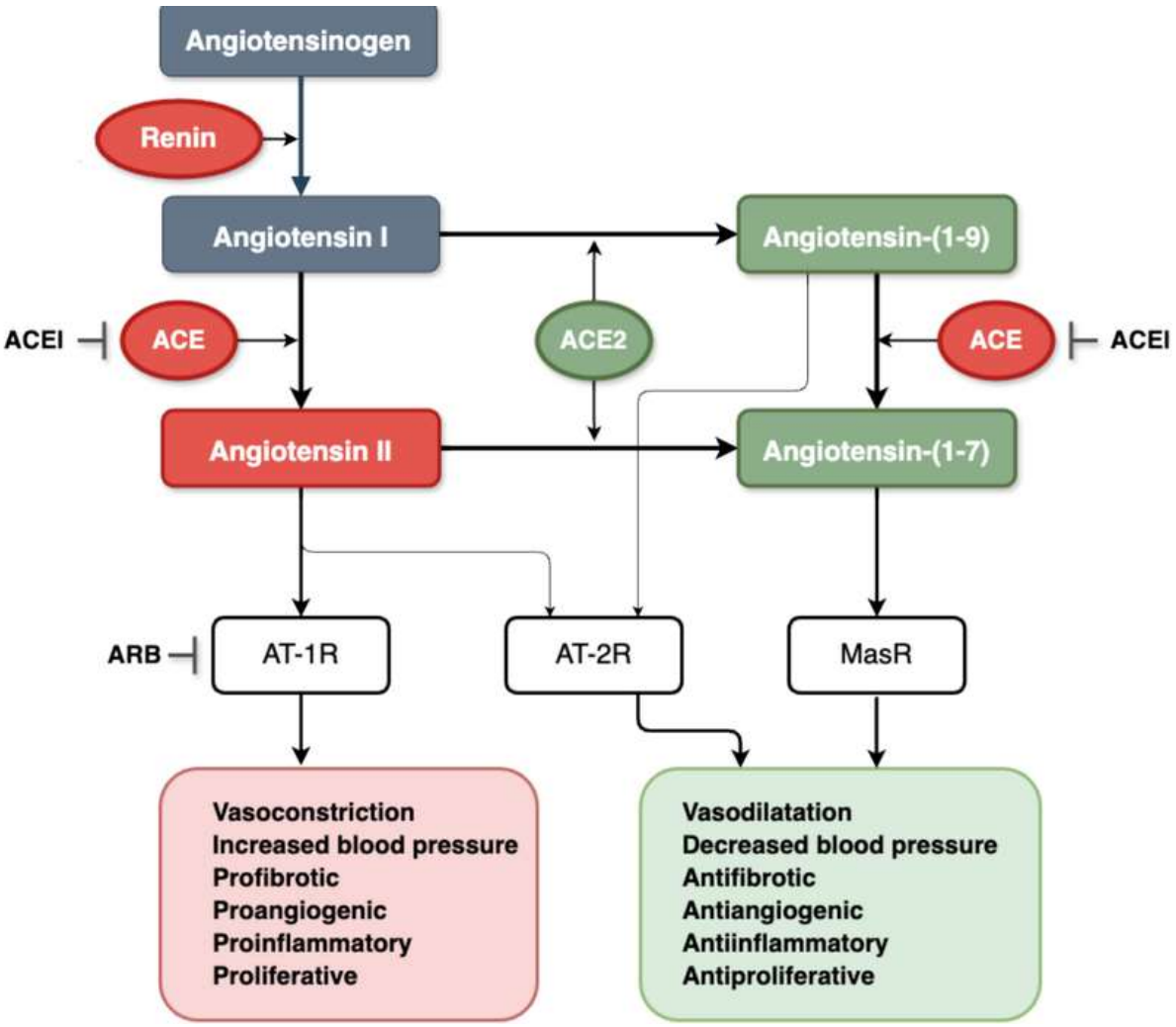

Figure 3 Renin-angiotensin-aldosterone system. AT1 and AT2 receptors and their effects

AT1 and AT2 receptor activation produce opposing effects:[75] [76]

- AT1 receptor activation leads to: vasoconstriction, increased blood pressure, profibrotic effects, proangiogenic effects, inflammatory effects, and proliferative effects.

- AT2 receptor activation leads to: vasodilation, decreased blood pressure, antifibrotic effects, antiangiogenic effects, anti-inflammatory effects, and antiproliferative effects.

The ELITE trial, which included 722 patients, had 370 receiving captopril and 352 receiving losartan. A 32% reduction in mortality and/or hospitalization rates was observed in patients taking losartan. Furthermore, losartan was better tolerated compared to captopril, allowing more patients to receive a higher dose of the medication until the end of the study.[77] However, these findings were followed by a second trial involving 3152 patients (ELITE II), which did not find the clinically significant differences between captopril and losartan that the first study had shown.[78]

The HEAAL (Heart failure Endpoint evaluation with Angiotensin II Antagonist Losartan) trial investigated whether a higher daily dose (150 mg) of the Angiotensin Receptor Blocker (ARB) losartan was superior to the standard daily dose (50 mg) in patients with symptomatic heart failure, reduced ejection fraction, and intolerance to ACE inhibitors. Over an average follow-up period of 4.7 years, the study demonstrated that the 150 mg dose significantly reduced the combined primary endpoint of all-cause death or hospitalization for heart failure by 10%. This reduction was primarily driven by a decrease in heart failure-related hospitalizations, despite an increased incidence of side effects such as hyperkalemia, hypotension, and renal dysfunction in the higher-dose group.[79] [80]

The VAL-HEFT (Valsartan Heart Failure Trial) showed that adding valsartan to standard heart failure treatment helped patients reduce the risk of death or the need for hospitalization due to heart failure. This benefit was particularly notable in patients who were not already receiving an ACE inhibitor. However, the study also suggested that taking valsartan alongside an ACE inhibitor and a beta-blocker might lead to more side effects. [81]

The CHARM program, which studied candesartan in 7601 patients with heart failure, is also worth noting. The program comprised three parts: CHARM-Alternative, CHARM-Added, and CHARM-Preserved.

- CHARM-Alternative showed the outcomes of candesartan in patients with low ejection fraction (EF ≤40%) and intolerance to ACE inhibitors.[82]
- CHARM-Added demonstrated the outcomes of candesartan in patients with low ejection fraction (EF ≤40%) who were already receiving ACE inhibitors.[83]
- CHARM-Preserved presented the outcomes of candesartan in patients with moderately reduced and preserved ejection fraction (EF ≥ 40%).[84]

Overall, the results of the CHARM program indicated the positive effects of candesartan in reducing cardiovascular mortality and rehospitalization rates in heart failure patients with low ejection fraction (EF ≤40%) It is important to note that a positive effect was not observed in the

CHARM-Preserved study, where a large proportion of patients were unable to continue the medication until the end of the study due to renal dysfunction, hyperkalemia, and hypotension.

Angiotensin-Converting Enzyme (ACE) Inhibitors

In patients with heart failure with reduced ejection fraction (HFrEF), the anatomical changes occurring in the left ventricle, which arise to compensate for myocyte death and neurohormonal activation, are collectively known as cardiac remodeling. This process is characterized by an increase in ventricular size, reduced contractility, and systolic dysfunction. To restore hemodynamic stability, the renin-angiotensin-aldosterone system (RAAS) becomes activated. The released angiotensin II causes systemic arterial vasoconstriction, stimulates sodium and water reabsorption, constricts smooth muscles, and promotes cellular proliferation. Prolonged activation of the RAAS leads to fibroblast proliferation, which progresses to myocardial fibrosis. It is precisely this elevated arterial pressure and the deposition of fibrotic tissue in the myocardium that drive the process of cardiac remodeling. Therefore, it is clear that in the short term, the RAAS plays an essential role in maintaining hemodynamic stability, but long-term, it contributes to the worsening of heart failure.

One of the medications that controls the RAAS is Angiotensin-Converting Enzyme (ACE) Inhibitors. ACE inhibitors are a class of medications primarily used to treat high blood pressure, heart failure, and to protect the kidneys in people with diabetes. They work by blocking the action of the ACE enzyme, which is responsible for converting angiotensin I to angiotensin II. By doing so, ACE inhibitors cause: Reduced Vasoconstriction; Decreased Aldosterone Production; Reduced Bradykinin Breakdown (This contributes to their blood pressure-lowering effect but can also cause side effects like a dry cough). Currently, the most commonly used ACE inhibitors include lisinopril, enalapril, ramipril, and captopril.[85]

The CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, published in 1987, was a groundbreaking study that provided the first unequivocal evidence of a survival benefit with ACE inhibitor therapy in patients with severe congestive heart failure (New York Heart Association Class IV). Patients with enlarged hearts (550 ml/m2 in women, 600 ml/m2 in men) were randomly assigned to receive either enalapril or a placebo. This multi-year study was prematurely stopped after just 1.5 years due to significant positive results. CONSENSUS showed that enalapril significantly reduced all-cause mortality by 31% at six months and 27% at one year. This reduction was primarily due to a decrease in the progression of heart failure and a reduction in sudden cardiac death. The study also demonstrated an improvement in heart failure symptoms. Essentially, CONSENSUS definitively established ACE inhibitors as a cornerstone therapy for severe heart failure, showcasing their ability to improve both survival and symptoms in this high-risk patient population. [86]

The SAVE (Survival And Ventricular Enlargement) trial, a landmark study published in 1992, demonstrated the benefits of ACE inhibitor therapy after myocardial infarction (heart attack).

The study enrolled patients with left ventricular dysfunction (ejection fraction 40% or less) following an acute heart attack, regardless of whether they had symptoms of heart failure. The study aimed to investigate the effect of captopril. The SAVE trial showed that captopril significantly reduced the risks of:

- All-cause mortality was reduced by 19% (p=0.019).
- Cardiovascular death, particularly sudden cardiac death, was reduced by 21% (p=0.014).
- The risk of recurrent myocardial infarction was reduced by 25% (p=0.012).
- The need for revascularization procedures (such as bypass surgery or angioplasty).

The main conclusion of the study was that initiating ACE inhibitor therapy early in patients with impaired cardiac function after a heart attack could prevent unfavorable cardiac remodeling and improve long-term survival and outcomes, even in the absence of overt heart failure symptoms. This established ACE inhibitors as standard treatment for post-myocardial infarction patients with reduced ejection fraction.[87] [88]

The ATLAS trial compared high and low doses of the ACE inhibitor lisinopril in heart failure patients. While the high dose did not significantly reduce mortality, it did lead to a reduction in hospitalization due to heart failure, though with a higher incidence of side effects. The study indicated that higher doses might offer some benefits in terms of hospital stays, but careful monitoring is required.[89] [90]

Despite their high efficacy, ACE inhibitors are characterized by many frequent side effects: dry cough, hyperkalemia, dizziness, fatigue, loss of taste, and so on. It is also important to note the frequent development of congenital malformations in pregnant women, which is why their use is forbidden throughout pregnancy.

Today, ACE inhibitors play a particularly significant role in asymptomatic patients with left ventricular systolic dysfunction and in symptomatic heart failure patients. [91]

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

A new class of medications has recently been approved for the pharmacological treatment of heart failure: the combination of sacubitril and valsartan is the first-generation Angiotensin Receptor-Neprilysin Inhibitor (ARNI). Neprilysin is an enzyme found in many different tissues. It breaks down various vasoactive peptides (natriuretic peptides, bradykinin, angiotensin I and II, glucagon-like peptide 1). With the addition of this new class, heart failure treatment strategy has shifted beyond simply inhibiting the renin-angiotensin-aldosterone system and sympathetic stimulation, ushering in an era of cardiac neurohormonal regulation.[92]

The PARADIGM-HF trial compared sacubitril/valsartan with enalapril in 8442 heart failure patients with reduced ejection fraction. The study was prematurely stopped due to the overwhelming benefit of ARNI. PARADIGM-HF showed that sacubitril/valsartan significantly reduced cardiovascular mortality by 20%, the frequency of hospitalizations for heart failure by 21%, and all-cause mortality by 16% compared to enalapril. Although a higher incidence of hypotension was observed in the ARNI group, patients experienced fewer serious renal side effects, less hyperkalemia, and a lower incidence of cough compared to the enalapril group.[93] This study also analyzed HbA1c levels in diabetic patients over 3 years and found that it was significantly lower in patients receiving sacubitril/valsartan than in those receiving enalapril.[94]

The TITRATION trial highlighted the safety of rapid titration of sacubitril/valsartan by comparing two titration methods: 1) Rapid titration - 100 mg twice daily for 2 weeks, then 200 mg; 2) Conservative titration - 50 mg twice daily for 2 weeks, then 100 mg twice daily for 3 weeks, and finally 200 mg twice daily.[95]

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