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CONDOLENCE MECHANISMS OF DRUGS USED IN THE DISEASE OF HEART FAILURE

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Annotation
Dear reader, in this article we want to provide information about the drugs used in heart failure, one of the important diseases that are now common . Heart failure — sometimes known as congestive heart failure — occurs when the heart muscle doesn't pump blood as well as it should. When this happens, blood often backs up and fluid can build up in the lungs, causing shortness of breath.Certain heart conditions, such as narrowed arteries in the heart (coronary artery disease) or high blood pressure, gradually leave the heart too weak or stiff to fill and pump blood properly.Proper treatment can improve the signs and symptoms of heart failure and may help some people live longer. Lifestyle changes — such as losing weight, exercising, reducing salt (sodium) in your diet and managing stress — can improve your quality of life. However, heart failure can be life-threatening. People with heart failure may have severe symptoms, and some may need a heart transplant or a ventricular assist device (VAD).One way to prevent heart failure is to prevent and control conditions that can cause it, such as coronary artery disease, high blood pressure, diabetes and obesity.

Keywords : Heart failure , aorte , drug , Nitrates , Digoxin

Heart failure (HF) is a syndrome of ventricular dysfunction .
Drug treatment of heart failure (HF) involves symptom relief with

- Diuretics
- Nitrates
- Digoxin

Drug treatment for long-term management and improved survival is with

- Angiotensin converting enzyme (ACE) inhibitors
- Beta-blockers
- Aldosterone antagonists
- Angiotensin II receptor blockers (ARBs)
- Angiotensin receptor/neprilysin inhibitors (ARNIs)
- Sodium-glucose cotransporter-2 inhibitors (SGLT2)
- Sinus node inhibitors

All patients should be given clear and explicit information about their drugs, including

- The importance of timely prescription renewal
- The importance of adherence to therapy
- How to recognize adverse effects
- When to contact their physician

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Selection of drugs for heart failure

Choice of drug depends on the type of heart failure along with individual patient characteristics. The most common classification of heart failure currently in use stratifies patients into

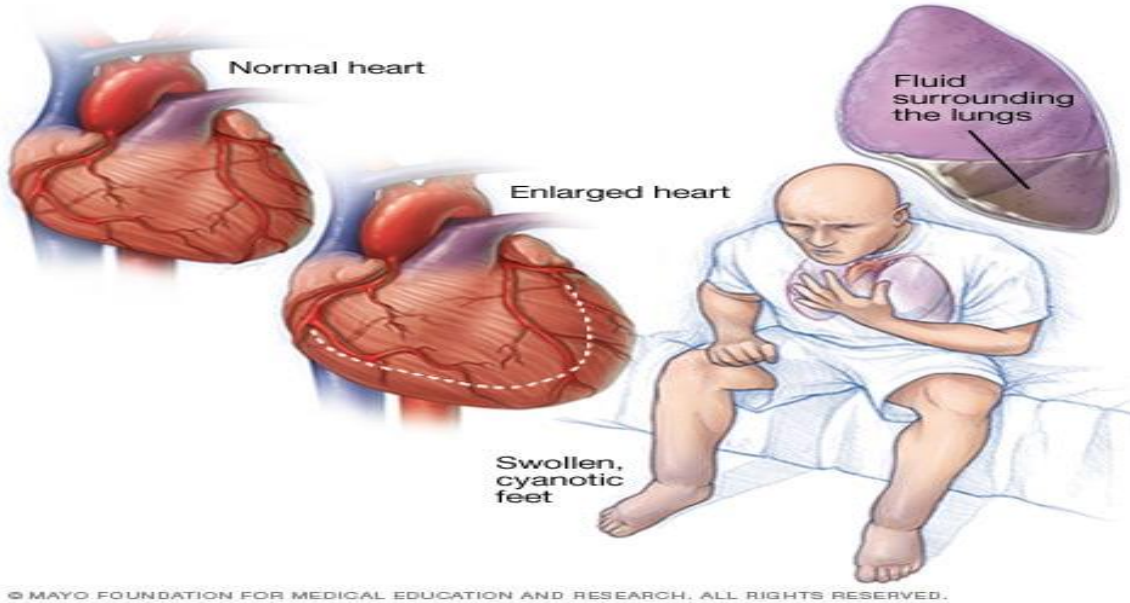
- Heart failure with reduced ejection fraction ("systolic HF")
- Heart failure with preserved ejection fraction ("diastolic HF")
- Heart failure with mildly reduced ejection fraction

Heart failure with reduced ejection fraction (HFrEF)

In HFrEF standard of care includes the following four classes of therapies, considered to be 'foundational therapies' for HFrEF management:

- Beta-blocker
- Renin-angiotensin-aldosterone system (RAAS) inhibitor(typically an ARNI, although an ACE inhibitor or ARB could also used if ARNI is not tolerated)
- Aldosterone antagonist
- SGLT2

These four drug classes have been studied and have shown benefit for long-term management of HFrEF. Therapy is typically titrated up to maximal tolerated doses. Patients are typically given a drug from each class. Because patients may already be taking one of these classes of drugs prior to developing heart failure, the order of therapy initiation and rate of up-titration are generally patient specific.



Addition of a sodium-glucose cotransporter-2 (SGLT2) inhibitor, either dapagliflozin or empagliflozin (1), has been shown to reduce morbidity and mortality when added to standard care in patients with elevated natriuretic peptide levels; benefit was similar in patients with and without diabetes.

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Other therapies are used in patient-specific settings (eg, sinus node inhibitors for lowering heart rate if patients cannot tolerate beta blockers).

Heart failure with preserved ejection fraction (HFpEF)

In HFpEF fewer drugs have been adequately studied. However, ACE inhibitors, ARBs, or aldosterone antagonists (mineralocorticoid receptor antagonists) are often used to treat HFpEF and/or associated comorbidities (such as hypertension and renal dysfunction), although survival benefit has not been demonstrated in clinical trials and, therefore, are not considered a standard of care.

ARNIs may reduce hospitalizations for heart failure but do not improve other outcomes.

In a recent clinical trial, the addition of the SGLT2 inhibitor empagliflozin to usual therapy was shown to reduce mortality and hospitalizations for HFpEF (2).

Beta blockers should be used only when there is another existing indication (eg, control of heart rate during atrial fibrillation, angina, following myocardial infarction). In patients with severe HFpEF (in contrast to HFrEF), lowering the heart rate (eg, with a beta-blocker) can exacerbate symptoms because they have a relatively fixed stroke volume due to severe diastolic dysfunction. In these patients, cardiac output (CO) is heart rate dependent, and lowering heart rate can thus lower CO at rest and/or with exertion.

In patients with infiltrative, restrictive, or hypertrophic cardiomyopathy, digoxin is not effective and may be harmful. In addition, vasodilator therapy may also be poorly tolerated and has not shown benefit in these patients.

Heart failure with mildly reduced ejection fraction (HFmrEF)

In HFmrEF there may be a specific benefit from ARNIs, although this possibility requires confirmation.

Patients with HFmrEF also benefit from the addition of an SGLT2 inhibitor such as empagliflozin to standard care.

Classes of Drugs for Heart Failure

Aldosterone antagonists

Because aldosterone can be produced independently of the renin-angiotensin system, its adverse effects are not inhibited completely even by maximal use of ACE inhibitors and angiotensin II receptor blockers (ARBs). Thus, the aldosterone antagonists (also termed mineralocorticoid receptor antagonists) are often used, particularly for patients with moderate to severe symptoms or signs of heart failure.

Typical drugs include spironolactone 25 to 50 mg orally once a day and eplerenone 25 to 100 mg orally once a day (does not cause gynecomastia in males). Aldosterone antagonists can reduce mortality, including from sudden death, in patients with left ventricular ejection fraction (LVEF) < 30% and chronic HF, or acute HF complicating acute myocardial infarction.

Potassium supplements should be stopped. Serum potassium and creatinine should be checked every 1 to 2 weeks for the first 4 to 6 weeks and after dose changes. Dose is lowered if potassium is between 5.0 and 5.5 mEq/L (5.5 mmol/L) and stopped if potassium is > 5.5 mEq/L (5.5 mmol/L), if creatinine increases above 2.5 mg/dL (220 micromol/L), or if ECG changes of hyperkalemia are present.

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Aldosterone antagonists should not be used in patients receiving both an ACE inhibitor and an ARB because of the high risk of hyperkalemia and renal dysfunction.

In patients with HFrEF, an aldosterone antagonist plus either an ACE inhibitor or an ARB is preferred over the combination of an ACE inhibitor and ARB.

In patients with HFpEF, spironolactone reduces hospitalization for heart failure and likely reduces cardiovascular mortality (1). Thus, aldosterone antagonists should be used in patients with HFpEF, particularly if they are volume overloaded and/or have a history of HF hospitalization. Loop diuretics can be minimized if necessary to accommodate the use of aldosterone antagonists.

Angiotensin converting enzyme (ACE) inhibitors

All patients with HFrEF should be given oral ACE inhibitors unless contraindicated (eg, by plasma creatinine > 2.8 mg/dL [> 250 micromol/L], bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, or previous angioedema due to ACE inhibitors).

ACE inhibitors reduce production of angiotensin II and breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone, and myocardial performance. Hemodynamic effects include

- Arterial and venous vasodilation
- Sustained decreases in LV filling pressure during rest and exercise
- Decreased systemic vascular resistance
- Favorable effects on ventricular remodeling

ACE inhibitors prolong survival and reduce HF hospitalizations. For patients with atherosclerosis and a vascular disorder, these drugs reduce the risk of myocardial infarction and stroke. For patients with diabetes, they delay onset of nephropathy. Thus, ACE inhibitors may be used in patients with diastolic dysfunction and any of these disorders.

The starting dose typically should be low (usually one fourth to one half of the target dose depending on blood pressure and renal function); the dose is gradually adjusted upward over 8 weeks as tolerated, then continued indefinitely. Usual target doses of representative drugs include enalapril 10 to 20 mg twice a day, lisinopril 20 to 30 mg once a day, and ramipril 5 mg twice a day; there are many others.

If the hypotensive effect (more marked in patients with hyponatremia or volume depletion) is troublesome, it can often be minimized by separating administration of other blood pressure–lowering drugs, reducing the dose of concomitant diuretics, using a longer acting ACE inhibitor (eg, perindopril), or giving the dose at bedtime. ACE inhibitors often cause mild to moderate reversible serum creatinine elevation due to vasodilation of the efferent glomerular arteriole. An initial 20 to 30% increase in creatinine is no reason to stop the drug but does require closer monitoring, slower increases in dose, reduction in diuretic dose, or avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs). Because aldosterone's effect is reduced, potassium retention (hyperkalemia) may result, especially in patients receiving potassium supplements. Cough occurs in 5 to 15% of patients, probably because bradykinin accumulates, but other causes of cough should also be considered. Occasionally, rash or dysgeusia occurs. Angioedema is rare but can be life threatening

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and is a contraindication to ACE inhibitors. Alternatively, ARBs can be used, although rarely cross-reactivity is reported. Both are contraindicated in pregnancy.

Serum electrolytes and renal function should be measured before an ACE inhibitor is started, at 1 month, and after each significant increase in dose or change in clinical condition. If dehydration or poor renal function due to acute illness develops, the ACE inhibitor dose may need to be reduced or the drug may be temporarily stopped.

In HFpEF, a randomized controlled trial of the ACE inhibitor perindopril demonstrated improved exercise capacity. It did not improve survival, although there was a high rate of crossover from placebo to ACE inhibitor in this trial (2). Given the very high prevalence of hypertension in HFpEF, it is reasonable to use an ACE inhibitor to control hypertension in these patients as these drugs may have secondary beneficial effects on exercise capacity in these patients.

Angiotensin II receptor blockers (ARBs)

These drugs are not demonstrably superior to ACE inhibitors but are less likely to cause cough and angioedema; they may be used when these adverse effects prohibit ACE inhibitor use.

In chronic HFrEF, ACE inhibitors and ARBs are likely equally effective. Usual oral target doses are valsartan 160 mg twice a day, candesartan 32 mg once a day, and losartan 50 to 100 mg once a day. Introduction, upward dose adjustment, and monitoring of ARBs and ACE inhibitors are similar. Like ACE inhibitors, ARBs can cause reversible renal dysfunction, and the dose may need to be reduced or stopped temporarily during an acute dehydrating illness.

Adding an ARB to a regimen of an ACE inhibitor, beta-blocker, and aldosterone antagonist is unlikely to be helpful and should be avoided given the risk of hyperkalemia. If a patient who is taking an ACE inhibitor or ARB is still symptomatic, an aldosterone antagonist should be started and/or an angiotensin receptor/neprilysin inhibitor (ARNI) should be used.

In HFpEF, a large randomized controlled trial of candesartan (3) demonstrated reduced number of hospitalizations for recurrent HF; however, hospitalization was a secondary endpoint. In another trial (4), irbesartan was not associated with any improvement in outcomes in HFpEF. Therefore, ARBs should be used in HFpEF only if they are already being used to treat hypertension, diabetic kidney disease, or microalbuminuria.

ARBs are contraindicated in pregnancy.

Angiotensin receptor/neprilysin inhibitors (ARNIs)

ARNIs are a new combination drug for the treatment of heart failure. They include an ARB and a newer class of drug, neprilysin inhibitors (eg, sacubitril). Neprilysin is an enzyme involved in the breakdown of vasoactive substances such as brain (B-type) natriuretic peptide (BNP) and other peptides. By inhibiting the breakdown of BNP and other beneficial vasoactive peptides, these drugs lower blood pressure, decrease afterload, and enhance natriuresis. Because neprilysin inhibitors increase BNP levels, NTproBNP levels (which are not increased by the drug) should be used instead to help diagnose and manage HF.

In HFrEF, a large randomized, controlled trial (5) compared sacubitril/valsartan to enalapril in patients with NYHA (New York Heart Association) class II through IV heart failure (see table NYHA

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Classification of Heart Failure). Sacubitril/valsartan reduced the primary endpoints of combined cardiovascular mortality or hospitalizations for HF; the number needed to treat was 21. Sacubitril/valsartan also reduced all-cause mortality. Thus, the ARNI sacubitril/valsartan should be considered in all patients with stable HFrEF, particularly those with NYHA class II or III symptoms on optimal guideline-directed medical therapy and who have elevated natriuretic peptide levels before starting treatment. Evidence supports early transition of patients from ACE/ARB to ARNI, even in the hospital setting where patients will experience less pulmonary congestion and may have fewer early readmissions.

There are 3 strengths of sacubitril/valsartan: 24/26 mg, 49/51 mg, and 97/103 mg, all are taken orally twice a day. The starting dose is 49/51 mg orally twice a day for patients previously taking an ACE inhibitor or ARB, and 24/26 mg for patients previously taking a low dose of an ACE inhibitor or ARB (eg, ≤ 10 mg enalapril daily) or in those patients who are ACE inhibitor/ARB naive or who have low/borderline blood pressure. ACE inhibitors must be discontinued 36 hours before initiation of sacubitril/valsartan. Patients previously taking an ARB can simply switch to sacubitril/valsartan without a washout period.

Complications associated with use of ARNI include hypotension, hyperkalemia, renal insufficiency, and angioedema. Sacubitril is coupled with valsartan (an ARB) because of the increased risk of angioedema with the use of sacubitril alone or in combination with an ACE inhibitor. For this reason, combined ACE/ARNI therapy is absolutely contraindicated.

In HFpEF, a phase 2 trial showed that the ARNI sacubitril/valsartan reduced NTproBNP levels at 12 weeks and left atrial volume at 36 weeks. The PARAGON HF study in a stable population of patients with HFpEF showed a non-significant reduction in death and hospitalization (6, 7). However, there may have been lower hospitalization rates—further study is needed.

Beta-blockers

In patients with HFrEF, beta-blockers, unless otherwise contraindicated (by asthma, 2nd- or 3rd-degree atrioventricular block, or previous significant intolerance), are critical for the treatment, and an important addition to ACE inhibitors in these patients. In HFrEF, beta-blockers are best started when the patient has no evidence of pulmonary congestion. Specific beta-blockers such as carvedilol and metoprolol succinate (ie, long-acting metoprolol) improve left ventricular ejection fraction, survival, and other major cardiovascular outcomes in patients with chronic HFrEF, including those with severe symptoms.

In patients with HFpEF, beta-blockers have not shown clear benefits in clinical trials. However, data from large registries have suggested that beta-blocker use is associated with improved outcomes in HFpEF despite the relatively high prevalence of chronotropic incompetence (ie, the inability to raise heart rate in response to increased exertional demand) in HFpEF. All major guidelines for heart failure recommend beta-blockade as first-line therapy for conditions where ventricular rate control is indicated (ie, control of ventricular rate with atrial fibrillation).

The starting dose should be low (one fourth of the target daily dose), then the dose is gradually increased over 8 weeks as tolerated. The acute negative inotropic effects of beta-blockade may initially

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cause cardiac depression and fluid retention. In such cases, a temporary increase in diuretic dose and slower upward titration of the beta-blocker dose is warranted. Tolerance may improve over time, and efforts should be made to reach target doses. Usual oral target doses are carvedilol 25 mg twice a day (50 mg twice a day for patients ≥ 85 kg), bisoprolol 10 mg once a day, and metoprolol 50 to 75 mg twice a day (tartrate) or 200 mg once a day (succinate extended-release). Carvedilol, a 3rd-generation nonselective beta-blocker, is also a vasodilator with alpha-blocking and antioxidant effects; it is the preferred and most widely studied beta-blocker but is more expensive in many countries. Some beta-blockers (eg, bucindolol, xamoterol) do not appear beneficial and may be harmful.

During a severe, acute decompensation, beta-blockers should not be started until patients are stabilized and have little evidence of fluid retention. For HFrEF patients with acute HF exacerbation already taking a beta-blocker, the dose should not be decreased or stopped unless absolutely necessary. Often the beta-blocker dose can be continued in patients with an acute HF exacerbation if the diuretic dose is temporarily increased.

In HFrEF, after initial treatment, heart rate and myocardial oxygen consumption decrease, and stroke volume and filling pressure are unchanged. With the slower heart rate, diastolic function improves. Ventricular filling returns to a more normal pattern (increasing in early diastole), which appears less restrictive. Improved myocardial function is measurable in some patients after 6 to 12 months but may take longer; ejection fraction (EF) and cardiac output (CO) increase, and LV filling pressure decreases. Exercise capacity improves.

Digoxin

Digoxin inhibits the sodium-potassium pump (Na+, K+-ATPase). As a result, it causes weak positive inotropy, reduces sympathetic activity, blocks the atrioventricular node (slowing the ventricular rate in atrial fibrillation or prolonging the PR interval in sinus rhythm), reduces vasoconstriction, and improves renal blood flow. Digoxin is excreted by the kidneys; elimination half-life is 36 to 40 hours in patients with normal renal function.

Digoxin has no proven survival benefit but, when used with diuretics and an ACE inhibitor, may help control symptoms and reduce the likelihood of hospitalization in patients with HFrEF. However, because of the availability of a large number of evidence-based treatments for HFrEF, digoxin use has dropped significantly and is reserved for patients with significant symptoms despite optimal treatment with other mortality lowering medications. Digoxin should not be used in HFpEF unless it is being used to control heart rate in concomitant atrial fibrillation or to augment RV function in patients with RV failure. Digoxin is most effective in patients with large LV end-diastolic volumes and a 3rd heart sound (S3). Acute withdrawal of digoxin may increase the hospitalization rate and worsen symptoms.

In patients with normal renal function, digoxin, 0.125 to 0.25 mg orally once a day depending on age, sex, and body size, achieves full digitalization in about 1 week (5 half-lives). More rapid digitalization can be achieved with digoxin 0.5 mg IV over 15 minutes followed by 0.25 mg IV at 8 and 16 hours or with 0.5 mg orally followed by 0.25 mg orally at 8, 16, and 24 hours. Prescription patterns vary widely by physician and by country, but in general, doses are lower than those used in the past, and a trough

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(8- to 12-hours post-dose) digoxin level of 0.8 to 1.2 ng/mL (1 to 1.5 nmol/L) is preferable. In addition, unlike in the treatment of atrial fibrillation, there is typically little reason to rapidly digitalize (ie, digoxin load) patients with HF. Thus, simply starting digoxin at 0.125 mg orally once a day (in patients with normal renal function) or digoxin 0.125 mg orally every Monday, Wednesday, and Friday (in patients with abnormal renal function) is sufficient in patients with heart failure.

Digoxin toxicity is a concern, especially in patients with renal dysfunction and perhaps in women. These patients may need a lower oral dose, as may older patients, patients with a low lean body mass, and patients also taking amiodarone. Digoxin has a narrow therapeutic window. The most important toxic effects are life-threatening arrhythmias (eg, ventricular fibrillation, ventricular tachycardia, complete atrioventricular block). Bidirectional ventricular tachycardia, nonparoxysmal junctional tachycardia in the presence of atrial fibrillation, and hyperkalemia are serious signs of digitalis toxicity. Nausea, vomiting, anorexia, diarrhea, confusion, amblyopia, and, rarely, xerophthalmia may occur. If hypokalemia or hypomagnesemia (often due to diuretic use) is present, lower doses and serum levels can still cause toxicity. Electrolyte levels should be monitored in patients taking diuretics and digoxin, so that abnormalities can be prevented if possible; potassium-sparing diuretics may be helpful.

When digoxin toxicity occurs, the drug should be stopped; electrolyte abnormalities should be corrected (IV if abnormalities are severe and toxicity is acute). Patients with severe toxicity are admitted to a monitored unit, and digoxin immune Fab (ovine antidigoxin antibody fragments) is given if arrhythmias are present or if significant overingestion is accompanied by a serum potassium of > 5 mEq/L (> 5 mmol/L). Digoxin immune Fab is also useful for glycoside toxicity due to plant ingestion. Dose is based on the steady-state serum digoxin level or total amount ingested. Ventricular arrhythmias are treated with lidocaine or phenytoin. Atrioventricular block with a slow ventricular rate may require a temporary transvenous pacemaker. Isoproterenol is contraindicated because it increases risk of ventricular arrhythmia.

Diuretics

Diuretics are given to all patients with HF (regardless of underlying ejection fraction) who have current or previous volume overload; dose is adjusted to the lowest dose that stabilizes weight and relieves symptoms.

Loop diuretics should be used initially for control of volume overload, but their dose should be reduced when possible in favor of aldosterone antagonists.

Commonly used loop diuretics include furosemide, bumetanide, and torsemide. The starting dose of these drugs depends on whether the patient has previously received loop diuretics. Common starting doses are: furosemide 20 to 40 mg orally once a day or twice a day, bumetanide 0.5 to 1.0 mg orally once a day, and torsemide 10 to 20 mg orally once a day. If needed, loop diuretics can be titrated up to doses of furosemide 120 mg orally twice a day, bumetanide 2 mg orally twice a day, and torsemide 40 mg orally twice a day based on response and renal function. Bumetanide and torsemide have better bioavailability than furosemide. If patients are

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switched between different loop diuretics, they should be placed on equivalent doses. Furosemide 40 mg is equivalent to bumetanide 1 mg, and both are equivalent to torsemide 20 mg.

In refractory cases, IV loop diuretics or metolazone 2.5 to 10 mg orally can be used for an additive effect. IV infusion of furosemide (5 to 10 mg/hour) or other loop diuretics may be helpful in selected patients with severe edema. A bolus dose of loop diuretic should be given before starting an IV infusion and before each increase in infusion rate.

Loop diuretics (particularly when used with metolazone) may cause hypovolemia with hypotension, hyponatremia, hypomagnesemia, and severe hypokalemia. The dose of diuretic required acutely can usually be gradually reduced; the target is the lowest dose that maintains stable weight and controls symptoms. When HF improves, the diuretic may be stopped if other drugs improve heart function and relieve HF symptoms. Using larger than required doses of diuretics lowers CO, impairs renal function, causes hypokalemia, and increases mortality. Serum electrolytes and renal function are monitored, initially daily (when diuretics are given IV) and subsequently as needed, particularly after a dose increase.

An aldosterone antagonist, either spironolactone or eplerenone, should be added early to offset the potassium-losing effects of higher-dose loop diuretics. Hyperkalemia may result, especially when ACE inhibitors or ARBs are also taken, so electrolytes must still be monitored, especially during a dehydrating illness that could cause renal dysfunction. Aldosterone antagonists may have particular benefit in chronic right ventricular failure, in which hepatic congestion results in elevated aldosterone levels as aldosterone metabolism is reduced. To reduce the risk of hyperkalemia, aldosterone antagonists should generally be given only to patients whose potassium level is < 5.0 mEq/L (< 5 mmol/L), serum creatinine is < 2.5 mg/dL (< 221 micromol/L), and GFR is > 30 mL/min/1.73 m^2. Furthermore, it should be noted that the equivalent dose of eplerenone is twice that of spironolactone (ie, spironolactone 25 mg = eplerenone 50 mg).

Thiazide diuretics are not normally used alone unless being given as treatment of hypertension; however, a thiazide diuretic may be added to a loop diuretic for additional diuresis and to reduce the loop diuretic dose. Hydrochlorothiazide, metolazone, and chlorthalidone can be used in this manner. Reliable patients are taught to take additional diuretic doses as needed when weight or peripheral edema increases. They should seek medical attention promptly if weight gain persists.

Vasopressin (antidiuretic hormone) receptor antagonists are not frequently used though they may be helpful in cases of severe refractory hyponatremia in patients with HF.

Sinus node inhibitors

There is an inward sodium/potassium current that travels through a certain gated channel (funny or "f" channel) in sinus node (cardiac pacemaker) cells located in the posterior right atrium. This current is sometimes referred to as the inward funny current (I_f). Inhibition of this current prolongs the time it takes to achieve critical spontaneous depolarization of pacemaker cells, and thus lowers the heart rate.

Ivabradine is an I_f channel blocker that acts at the sinus node to slow the heart rate. Since the receptors are present only in cardiac pacemaker cells, these drugs have no other cardiac effects (ie

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they do not directly affect contractility), and are not useful for treatment in patients who are not in sinus rhythm. Ivabradine is currently recommended for use in HFrEF patients who have symptomatic HF, normal sinus rhythm, and heart rate > 70 beats/minute despite guideline-directed medical therapy (which should include beta-blockers). Typically, patients who may benefit from ivabradine are those with HFrEF who have NYHA (New York Heart Association) class II or class III symptoms (see table NYHA Classification of Heart Failure) and heart rate > 70 beats/minute who are at target beta-blocker dose or cannot tolerate a further increase in beta-blocker dose (8).

Initial dose of ivabradine is 2.5 to 5 mg orally twice a day, titrated at 2-week intervals to a heart rate of 50 to 60 beats/minute; maximum dose is 7.5 mg twice a day.

Ivabradine is currently the only drug in this class.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

SGLT2 inhibitors are used in treatment of diabetes to block glucose reabsorption, thus causing glycosuria and lowering plasma glucose. They may also have effects on the myocardium and vasculature. These drugs had previously been shown to prevent the onset of heart failure in patients with type 2 diabetes. One member of this class, dapagliflozin, was shown to improve symptoms and quality of life and decrease hospitalization and mortality in patients with HFrEF when added to standard care in patients with elevated natriuretic peptide levels; benefit was similar in patients with and without diabetes (9). In a recent clinical trial, the addition of the SGLT2 inhibitor empagliflozin to usual therapy was shown to reduce hospitalizations and death for patients with HFpEF, with or without diabetes (10).

Dapagliflozin and empagliflozin may be given 10 mg orally once a day. With treatment, there is a mild (10 to 15%) reduction in estimated glomerular filtration rate (eGFR) which does not progress, glucosuria, and a small reduction in body weight. Risks include genital fungal infection, and in patients with diabetes, a very small risk of hypoglycemia and diabetic ketoacidosis. These drugs are generally not indicated in patients with type I diabetes, low blood pressure, low eGFR (< 30 mL/min/1.73 m^2), or rapidly worsening renal function.

Other SGLT2 inhibitors (eg, canagliflozin, ertugliflozin) have not been studied directly in HF, but secondary analysis of studies in diabetes suggest they may also be beneficial.

Vasodilators

Hydralazine plus isosorbide dinitrate may help patients truly intolerant of ACE inhibitors or ARBs (usually because of significant renal dysfunction), although limited studies show long-term benefit of this combination. However, in patients of African ancestry this combination, when added to standard therapy, has been shown to reduce mortality and hospitalization, and improve quality of life. As vasodilators, these drugs improve hemodynamics, reduce valvular regurgitation, and increase exercise capacity without causing significant renal impairment.

When used instead of ACE/ARB therapy, hydralazine is started at 25 mg orally 4 times a day and increased every 3 to 5 days to a target total dose of 300 mg/day, although many patients cannot tolerate > 200 mg/day because of hypotension. Isosorbide dinitrate is started at 20 mg orally 3 times a day (with a 12-hour nitrate-free interval) and increased to a target of 40 to 50 mg 3 times a day.

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Whether lower doses (frequently used in clinical practice) provide long-term benefit is unknown. In general, vasodilators have been replaced by ACE inhibitors, which are easier to use, are usually better tolerated, and have greater proven benefit.

When added to ACE/ARB therapy, hydralazine-nitrate therapy may benefit patients of African ancestry with HFrEF. In this case, the starting dose is hydralazine 37.5 mg and isosorbide dinitrate 20 mg orally three times a day, with the maximum dose 75 mg and 40 mg three times a day. These doses are also available as a fixed-dose combination. The decision to add or substitute hydralazine-nitrate therapy to an ACE/ARB in patients of African ancestry with HF is patient specific and frequently determined by drug tolerance and symptom burden. In general, RAAS inhibitor therapy (ACE, ARB, or ARNI) should be used in this population, if tolerated.

Nitrates alone can relieve HF symptoms in patients with HFrEF; patients can be taught to use sublingual nitroglycerin spray as needed for acute dyspnea and a transdermal patch for nocturnal or exertional dyspnea. In HFrEF, nitrates are safe, effective, and well tolerated and are particularly helpful in patients with HF and angina. Adverse effects include hypotension and headache. Isosorbide mononitrate has been tested in HFpEF (11), where it was shown to be associated with increased adverse effects (eg, headache) and reduced physical activity. Thus, routine use of long-acting nitrates should be avoided in HFpEF.

Other vasodilators such as calcium channel blockers are not used to treat LV systolic dysfunction. Short-acting dihydropyridines (eg, nifedipine) and nondihydropyridines (eg, diltiazem, verapamil) may be deleterious. However, amlodipine and felodipine are better tolerated and may be useful for patients with HF and associated angina or hypertension. Both drugs may cause peripheral edema; rarely, amlodipine causes pulmonary edema. Felodipine should not be taken with grapefruit juice, which significantly increases plasma levels and adverse effects by inhibiting cytochrome P-450 metabolism. In patients with HFpEF, dihydropyridine calcium channel blockers such as amlodipine may be used as needed to treat hypertension or ischemia; nondihydropyridines such as diltiazem or verapamil may be used to control ventricular rate in atrial fibrillation. Verapamil is often used in hypertrophic cardiomyopathy.

Other drugs

Various positive inotropic drugs have been evaluated in heart failure but, except for digoxin, they increase mortality risk. These drugs can be grouped as adrenergic mode of action (norepinephrine, epinephrine, dobutamine, dopamine) or nonadrenergic (enoximone, milrinone, levosimendan [calcium sensitizers]). Regular outpatient IV infusions of inotropes (eg, dobutamine) were previously tried but found to increase mortality and are not recommended. However, outpatient continuous infusions of inotropes such as dobutamine or milrinone can be used for palliative purposes in patients with severe HFrEF.

Vericiguat is an oral soluble guanylate cyclase stimulator which enhances the cyclic guanosine monophosphate (GMP) pathway and sensitizes soluble guanylate cyclase to endogenous nitric oxide, resulting in pulmonary vasodilation. A clinical trial in symptomatic chronic HFrEF patients with evidence of worsening HF demonstrated reduced cardiovascular mortality or HF hospitalizations for

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patients randomized to receive vericiguat (12). Vericiguat may therefore be an option to improve outcomes for HFrEF patients with worsening HF symptoms.

LITERATURE

1. Pitt B, Pfeffer MA, Assmann SF, et al: Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 370:1383–1392, 2014. doi: 10.1056/NEJMoa1313731
2. Cleland JG, Tendera M, Adamus J, et al: The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 27:2338–2345, 2006. doi: 10.1093/eurheartj/ehl250
3. Yusuf S, Pfeffer MA, Swedberg K, et al: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 362:777, 2003. doi: 10.1016/S0140-6736(03)14285-7
4. Massie BM, Carson PE, McMurray JJ, et al: Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 359:2456–2467, 2008. doi: 10.1056/NEJMoa0805450
5. McMurray JJ, Packer M, Desai AS, et al: Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 371:993–1004, 2014. doi: 10.1056/NEJMoa1409077
6. Solomon SD, McMurray JJ, Anand IS, et al: Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 381:1609–1620, 2019. doi: 10.1056/NEJMoa1908655
7. McMurray JJV, Jackson AM, LAM CSP, et al: Effects of sacubitril-valsartan Versus valsartan in women compared with men with heart failure and preserved ejection fraction: Insights From PARAGON-HF. *Circulation* 41(5):338–351, 2020. doi: 10.1161/CIRCULATIONAHA.119.044491
8. Swedberg K, Komajda M, Bohm M, et al: Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 376(9744):875–885, 2010. doi: 10.1016/S0140-6736(10)61198-1
9. McMurray JJV, Solomon SD, Inzucchi SE, et al: Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 381(21):1995–2008, 2019. doi: 10.1056/NEJMoa1911303