

Pharmacokinetics, Mechanism of Action, and Adverse Effects of the Main Drugs Used to Treat Heart Failure: A Practical Overview for the Clinical Cardiologist

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Angiotensin-converting enzyme inhibitors (ACEI)

Mechanism of action

The renin-angiotensin-aldosterone system (RAAS), and particularly angiotensin II, plays a crucial role in the pathophysiology of Heart Failure (HF), perpetuating cardiac remodeling, both on the cardiac structure level (provoking myocyte and fibroblast cell proliferation) and on the preload level (because of sodium retention and increased intravascular volume in the circulation), and in peripheral vascular resistance, by stimulating direct vasoconstriction and increased sympathetic discharge.¹

As the name of the ACEI class implies, these drugs act to inhibit angiotensin-converting enzymes (ACEs) I and II, blocking the effects described above. This drug class also has an additional effect; ACE acts on a range of different substrates, including inactivation of bradykinin and other vasodilator peptides, and when this inactivation effect is blocked, there is an additional effect, reducing afterload.²

Pharmacokinetics

The ACEIs achieve bioavailability either in the form of the drug itself or as a pro-drug, depending on which pharmaceutical is chosen. In general, their metabolism is hepatic, but liver dysfunctions do not cause significant changes to their activation.² However, creatinine clearance abnormalities may preclude their use because they are excreted via this pathway and can contribute to maintenance of renal dysfunction.¹

Enalapril is the principal member of this group used to treat HF. Its active metabolite is enalaprilat, which achieves maximum concentration 3 to 4 hours after administration and has a plasma half-life of around 11h. The maximum recommended dose of this medication is 40mg per day. It is recommended that enalapril should be introduced gradually and increased in accordance with the patient's tolerance, both in terms of symptoms of hypotension and in terms of possible decline in renal function.¹⁻⁵

Keywords

Heart Failure; Review; Pharmacology; Practical View

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Adverse effects

The principal effects to be considered are hyperkalemia, allergies, coughing, and angioedema. The last two of these are related to increased bradykinins and other prostaglandins. These drugs are contraindicated in pregnant women because of the possibility of inducing kidney damage in the fetus and should therefore also be avoided in women of fertile age.³

Angiotensin ii receptor blockers (ARBs)

Mechanism of action

Based on what was described above in relation to the role played by angiotensin II in cardiac remodeling, ARBs act to block this effect at the level of the AT1 receptor, in contrast to the ACEIs which act on production of this peptide. In this case, conversion of angiotensin I into angiotensin II follows its normal cycle, i.e., there is an elevated serum angiotensin II level, but its AT1 receptors will be blocked.¹ It should be remembered that there is also an AT2 receptor that is not blocked by the ARBs, which is one of the features that lead to a degree of preference for the ACEIs over this group. Bearing in mind that ACE acts normally in patients who are taking these drugs, inactivation of bradykinin and other vasodilator peptides continues as normal, meaning that this group has lower vasodilatory power and fewer related side-effects.²

Pharmacokinetics

This class also has presentations in the form of drug or pro-drug, which are absorbed and activated in the gastrointestinal tract and cleared renally and can precipitate deterioration of creatinine clearance.² Losartan, a member of this group, has an active metabolite with a half-life in the range of 3 to 4h,² with an initial dose of 50mg per day, targeting a daily maximum dose of 150mg.³

Adverse effects

Adverse effects are similar to those of the ACEIs, with the exception of coughing and angioedema since, as described above, they do not affect bradykinin metabolism.⁶

Practical Aspects (of use of ACEIs and ARBs):³

- Intolerance of ACEIs is defined as presence of persistent and debilitating coughing (which occurs in approximately 10 to 20% of cases) or occurrence of angioedema (a rare finding: < 1%). Use of ARBs is an alternative option in these cases. Rates

of other adverse effects, such as hypotension, hyperkalemia, or renal dysfunction, are similar for ACEIs and ARBs. In cases of persistent and recurrent hyperkalemia and/or loss of renal function with ACEIs/ARBs, an alternative vasodilator therapy should be considered (in general, a combination of nitrate and hydralazine).

- Due to the risk of deterioration of renal function, hyperkalemia, and arterial hypotension, ACEIs/ARBs should be introduced at low doses (especially in patients with borderline blood pressure) and titrated progressively, until the target dose is attained, guaranteeing the benefits documented in large multicenter clinical trials.

- An increase of up to 50% over baseline creatinine, or an absolute value of up to 3 mg/dL, or an estimated creatinine clearance > 25 mL/min/m² is acceptable without requiring that drug dosages be reduced (ACEI or ARB). In these cases, it is recommended to maintain strict surveillance of renal function and potassium levels. If potassium exceeds 5.5 mEq/L, or creatinine exceeds 3.5 mg/dL, or clearance is below < 20 mL/min/m², then withdrawal of the ACEI or ARB should be considered.

- Combinations with ACEI and ARB should not be administered to patients taking aldosterone antagonists because of the risk of side effects, especially hyperkalemia.

Angiotensin receptor-neprilysin inhibitor (ARNI - Sacubitril/Valsartan):

Mechanism of action

Still with regard to the pathophysiology of Heart Failure, we need to focus on the effects of the natriuretic peptides – brain, atrial, and type C – which are endogenous hormones capable of stimulating natriuresis, vasodilation, and diuresis. Brain and atrial natriuretic peptides have the greatest effects on the many different factors that determine heart failure and are released when ventricular and atrial muscles, respectively, are distended. In addition to the effects described above, they can also reduce the effects of angiotensin II, contributing to block the renin-angiotensin-aldosterone system. These peptides have short half-lives and are metabolized at the renal, hepatic, and pulmonary levels by neutral endopeptidase or neprilysin.^{4,5} Use of these drugs alone had no impact on morbidity or mortality rates of patients with HF, but, according to the PARADIGM – HF study, the combination of sacubitril (oral neprilysin inhibitor) with valsartan (angiotensin receptor blocker) achieved greater reductions in hospital admissions and improvements in quality of life and mortality among patients with HF than ACEI, previously considered the first line of treatment.^{7,8}

Pharmacokinetics

Sacubitril is a pro-drug metabolized at the hepatic level and excreted via the kidneys, in common with valsartan, so it should also be avoided in patients with impaired creatinine clearance.⁵ Treatment with this drug should be optimized by degrees, observing which drugs the patient

had been taking previously (ACEI or ARB) to minimize side effects and interactions with them. The initial dose is 24/26mg³ or 49/51mg⁶ twice a day, depending on the reference followed, progressing to a maximum dose of 97/103mg twice a day.

Adverse effects

Beyond the adverse effects of valsartan (and of ARBs in general) already known, there is also a possibility of hypersensitivity to sacubitril and patients with borderline blood pressure tend to have more episodes of hypotension when taking sacubitril/valsartan. It should be noted that for patients who have been taking an ACEI, a 36h period without medications should be allowed to elapse before starting them on sacubitril/valsartan, because of a risk of angioedema. Patients on an ARB do not need to undergo this pause in treatment.^{4,5}

Practical aspects

- Test renal function and electrolytes.⁹
- Drug tolerability, side effects, and monitoring with laboratory tests are similar with ARNI to with ACEIs or ARBs, already mentioned above.⁹
- Serum levels of urea, creatinine, and potassium should be monitored 1 to 2 weeks after starting treatment and after titrations.⁹
- If the patient had been taking ACEI and it is decided to change to ARNI, it is necessary to allow 36h to elapse without taking an ACEI before starting on sacubitril/valsartan. This washout period is to reduce the risk of angioedema and no washout is needed to change from an ARB to an ARNI.¹⁰

Beta blockers

Beta-blockers (BB) are first-line drugs for treatment of heart failure with reduced ejection fraction (HFrEF), because they yield clinical benefits observed in overall mortality, death from HF, and sudden death, in addition to improving symptoms and reducing rates of hospital readmissions for HF.¹¹⁻¹⁴ Of the options available, those that have demonstrated consistent results are Bisoprolol,¹¹ Metoprolol Succinate,¹² Carvedilol.¹³ Additionally, Nebivolol was tested in patients with HF over the age of 70 years and reduced the primary clinical outcome (total mortality and cardiovascular hospital admissions), but did not have a statistically significant impact on total mortality in isolation.¹⁵ (Chart 1)

Reverse remodeling, increased left ventricle ejection fraction (LVEF), and the consequent improvement in HF symptoms occur just a few weeks or months after introduction of the BB. It is important to start treatment with low doses, with progressive increases every 2 weeks, depending on tolerability (monitoring bradycardia and worsening of HF symptoms). If symptoms are accentuated, adjustments of diuretics and vasodilators should be attempted before reducing dosage or suspending the BB. BB are also indicated for patients with asymptomatic left ventricle (LV) dysfunction and for control of ventricular frequency in patients with HFrEF and chronic atrial fibrillation (AF).^{3,16}

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Chart 1 – Recommendations from the Brazilian Heart Failure Guidelines – 2018.³

Bisoprolol, carvedilol, and metoprolol succinate for symptomatic LV dysfunction to reduce morbidity and mortality. Class/Evidence Level (EL): I/A

Nebivolol for symptomatic LV dysfunction in patients > 70 years of age. Class/EL: IIB/B

LV: left ventricle.

Mechanism of action and pharmacokinetics

Since the catecholamines exert positive chronotropic and inotropic actions, antagonists of their receptors do the opposite, reducing heart rate and myocardial contractility. When tonic stimulation of the receptors is low, this effect is correspondingly modest. However, when the sympathetic nervous system is activated, such as during exercise or stress, the receptor antagonists attenuate the expected increase in heart rate.²

All of the clinically available BB are competitive antagonists. Non-selective Beta-blockers block the β_1 and β_2 receptors, whereas cardioselective types have a predilection for β_1 . Some selective β_1 antagonist drugs with clinical applications in HF are: Metoprolol, Bisoprolol and Nebivolol. They have oral presentations and good bioavailability; Metoprolol and Bisoprolol have half-lives from 3 to 4 hours, while Nebivolol has a half life of 10 to 30 hours.^{2,17}

These drugs antagonize β_1 receptors at doses 50 to 100 times lower than those needed to block β_2 receptors. This cardioselectivity is significant at low doses but is lost at elevated doses.^{2,17} Consequently, patients with HF and some degree of lung disease, including asthmatics, can take BBs, but those with greater β_1 selectivity (such as bisoprolol and nebivolol) are preferred.^{3,7}

With regard to Carvedilol, this is a non-selective BB that antagonizes β_1 receptors and also α_1 receptors, blockage of which produces peripheral vasodilation, reducing arterial blood pressure. This drug is also well-tolerated via oral route and its plasma half-life is from 7 to 10 hours.^{2,13}

Adverse effects

In the cardiovascular system, bradycardia is the normal response to β blockade, but β antagonists may cause bradyarrhythmia in patients with partial or complete atrioventricular conduction defects. Particular caution should be exercised with patients who are being treated with other drugs, such as verapamil or antiarrhythmics, which can impede sinoatrial node function and adequate atrial-ventricular conduction.⁷ In cases of atrioventricular blockade, other drugs that act on the atrioventricular node, such as digoxin and amiodarone, should be withdrawn first.³

The most important adverse effect on pulmonary function is caused by β_2 receptor blockade, in the bronchial smooth muscle. This can be particularly dangerous in patients with bronchospastic disease.²

Practical Aspects

- The beneficial results of BBs may only become apparent after several months of use and in some patients they occur later still (after 12 months).³

- Some patients may report discrete functional deterioration at the start of treatment with BBs, but should be encouraged to continue using the medication.³

- The majority of patients with HFrEF, particularly those at less advanced functional classes, can be treated with BBs by physicians who are not specialists in HF.³

- Patients at more advanced functional classes should be reassessed with more frequent visits when started on BBs and may benefit from assessment by a specialist in HF.³

- Patients with lung disease – and even asthmatics – can be treated with BBs, giving preference to those with greater selectivity β_1 (such as bisoprolol and nebivolol).^{3,7}

- If atrioventricular blockade occurs, the first response should be to reduce or withdraw other drugs that act on the atrioventricular node, such as digoxin and amiodarone.³

- Transitory fluid retention may occur at initiation of beta blockers or on uptitration, which may require reevaluation of diuretic dosages.³

Mineralocorticoid receptor antagonists

The biological effects of aldosterone have significant repercussions for the pathophysiology of Heart Failure, making it extremely important to reduce this mineralocorticoid as part of treatment for the condition.¹⁸

In HF, these medications are indicated for symptomatic LV dysfunction, at New York Heart Association (NYHA) functional classes II to IV, combined with standard treatment with ACEI or ARB and BB,³ with a maximum evidence level (I-A).

Eplerenone has a more selective action, but is not available on the Brazilian market, although its results can be extrapolated to spironolactone.¹⁹

Mechanism of action and Pharmacokinetics

When aldosterone binds to Mineralocorticoid Receptors (MR) located in the final portion of the distal tubule and in the collecting duct, it induces synthesis of Aldosterone Induced Proteins (AIP), which has the biological consequences of inducing retention of sodium and water, in addition to excretion of K^+ and H^+ .²

Mineralocorticoid receptor antagonists (MRAs - spironolactone and eplerenone) competitively inhibit binding of aldosterone to MR and are not capable of inducing formation of AIP, thereby blocking the effect of aldosterone in the body, which improves endothelial function and nitric oxide bioavailability, with possible antisclerotic effects, in addition to reduction of myocardial fibrosis having been demonstrated.²⁰

Adverse effects

Since these are diuretic and potassium-sparing drugs, they may have side effects such as hypotension, dehydration, and hyponatremia, in addition to hyperkalemia, so it is necessary to monitor potassium levels and regularly test renal function.¹⁹ MRAs should therefore be avoided in patients with > 2.5 mg/dL or hyperkalemia. Additionally, spironolactone also has an antiandrogenic effect and inhibits steroidogenesis, which can cause gynecomastia and loss of libido,²⁰ which are not as common with eplerenone, because it is more selective.

Practical aspects

- Check renal function and electrolytes (especially K^+), particularly after initiating treatment/increasing dosage.⁹
- Consider titration of dosage after 4 to 8 weeks.
- If $K^+ > 5.5$ mmol/L or Creatinine > 2.5 mg/dL and glomerular filtration rate (GFR) < 30 mL/min/1.73 m², halve the dosage and monitor blood tests.⁹
- If $K^+ > 6.0$ mmol/L or Creatinine > 3.5 mg/dL and GFR < 20 mL/min/1.73 m², withdraw MRAS immediately and consult a specialist.⁹

SGLT2 inhibitors

Recently, major advances have been achieved in relation to antidiabetic medications and cardiovascular risk. This has yielded a new approach to treatment of HFrEF, different from conventional blockage of the system – the sodium-glucose cotransporter 2 inhibitors (SGLT2i).¹ These drugs initially demonstrated their cardiovascular safety in patients with type 2 Diabetes Mellitus (DM2), with beneficial effects, such as reduction of cardiovascular events, cardiovascular mortality, and hospital admissions for HF, using empagliflozin.² Later, other studies revealed benefits of this class, extending to Canagliflozin,³ Dapagliflozin and Empagliflozin, including in patients without diabetes^{4,5} and, finally, to Sotagliflozin (not available in Brazil).⁶ (Chart 2)

Mechanism of action and Pharmacokinetics

The mechanisms underlying cardiovascular protection and the renal effects of SGLT2 inhibitors in patients with and without DM2 are still not entirely understood,

although several mechanisms have been proposed.²⁰ These new drugs act to inhibit glucose reabsorption in the renal tubules, by inhibiting the SGLT2 receptors in the distal convoluted tubule (DCT), provoking glycosuria. Reduction of glycemia is also related to natriuresis, osmotic diuresis, modest weight loss, increased hematocrit, and reduction of arterial blood pressure. The hemodynamic effects occur early, since as endothelial function and vasodilation improve, there are also reductions in preload and afterload and also in cardiac fibrosis.²¹

These drugs have shown a high affinity for SGLT2, low affinity for SGLT1 (which guarantees better tolerability), good oral route bioavailability, and prolonged life, permitting administration of an oral dose once a day. Additionally, metabolism does not involve active metabolites, so they also have a limited drug interaction profile. Finally, no clinically relevant changes in the pharmacokinetics of these drugs have been observed in patients with DM2, kidney failure, or mild/moderate liver failure.²²

Adverse effects

In general, SGLT2 inhibitors have a good tolerability profile and are not associated with many adverse effects, beyond a small chance of developing hypoglycemia, despite the glycosuria.¹⁰ The glycosuria increases the risk of infections of the genitourinary tract, especially genital infections (a 4% increase compared to placebo), and infections of the urinary tract (a 1% increase in relation to placebo).²² However, it is valid to point out that, in general, these are not severe infections and can be easily managed with antibiotic therapy alone.²²⁻²⁴ Finally, some concerning observations that need to be confirmed in clinical trials and must be investigated more intensely involve a potentially worrying trend for an increased incidence of breast and bladder cancer – clearly this must be investigated more intensely in clinical trials.^{22,25}

Practical Aspects

- Test renal function when starting treatment and monitor it regularly. It is known that GFR reduces slightly after starting treatment, but SGLT2i appear to offer kidney protection.⁹
- Monitor glycemia regularly, primarily when the patient is diabetic. Consider modifying other diabetic drugs.⁹

Chart 2 – Recommendations from the Brazilian Heart Failure Guidelines – 2021, for use of SGLT2 inhibitors in treatment of HFrEF.³

Dapagliflozin or Empagliflozin are indicated in patients with symptomatic HFrEF, diabetic or not, with maximum optimized dose of BB, aldosterone antagonist, ACEI/ARB, or ARNI, to reduce cardiovascular outcomes and progression of renal dysfunction. Class/Evidence level (EL): I/A

Canagliflozin, Dapagliflozin, or Empagliflozin for prevention of hospital admissions for HF in patients with DM2 who have cardiovascular risk factors for atherosclerosis or established atherosclerotic cardiovascular disease. Class/EL: I/A

Dapagliflozin or Empagliflozin as initial antidiabetic medication, combined or not with metformin in patients with HFrEF. Class/EL: I/A

Dapagliflozin or Empagliflozin in patients with HFrEF for prevention of reduction of renal function in patients with and without diabetes, with TGF > 20 mL/min/1.73 m². Class/EL: IIa/A

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blockers; DM2: type 2 diabetes mellitus; GFR: glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

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Nitrates and Hydralazine

Mechanism of action

The combination of hydralazine and nitrates has arterial and venous vasodilatory effects. This combination is able to reduce preload and afterload, reduce atrial and left ventricular wall tension, improve LV ejection fraction, and induce reverse remodeling, having demonstrated favorable effects on left ventricular function and HF-associated mortality.²⁶ Additionally, the combination maintains a balance between nitric oxide and reactive oxygen species (ROS), which is important for maintenance of cardiovascular health.³ The V-HeFT I study²⁷ confirmed these beneficial effects, with reduction in mortality compared with placebo, but the combination did not surpass the benefit of ACEIs, as was later demonstrated in the V-HeFT II study.²⁸

However, according to the A-HeFT (African-American Heart Failure Trial) study, hydralazine and nitrate demonstrated considerable additional benefits in self-declared black patients, at NYHA functional class III-IV who were already on standard treatment, with a 33% reduction in hospital admissions and 43% drop in total mortality.²⁹

Pharmacokinetics

In the A-HeFT study, the initial dose, available as a fixed dose, was 37.5 mg of hydralazine and 20 mg of isosorbide dinitrate, oral route, 3 times/day, with a maximum dose of 75 mg and 40 mg, 3 times/day, depending on tolerance and side effects. In Brazil, there is no fixed dose available and the initial dose suggested is 25 mg hydralazine and 10 mg of nitrate, 3 times a day, increasing progressively up to 100 mg per day of hydralazine and 40 mg per day of nitrate, also 3 times a day, or up to the maximum dose tolerated.²⁰

Side effects

The most common side effects of nitrate are related to vasodilation: orthostatic hypotension, tachycardia, and pulsating headaches. The most frequent side effects of hydralazine are headaches, nausea, anorexia, palpitations, diaphoresis, and rubor, and when given in higher doses there is a small chance of development of a syndrome similar to lupus erythematosus.¹

Practical Aspects

- Introduction of vasodilators may be indicated for patients who exhibit deterioration of renal function and/or hyperkalemia when taking ACEI/ARBs, for those who do not improve when put on optimized drug therapy, or in whom there is documented persistence of signs of elevated peripheral resistance.³
- Nitrates alone may be useful to relieve orthopnea, paroxysmal nocturnal dyspnea, effort dyspnea, or angina, but continuous use is associated with development of tolerance.¹⁰

Ivabradine

In 1987, the Framingham Study showed that heart rate (HR) was associated with all causes of cardiovascular and coronary mortality over 30 years of follow-up.³⁰ A review of the literature

indicated that elevated HR is associated with worse prognosis in HF and can be considered a treatment target.³¹

Mechanism of action

As such, Ivabradine can be considered part of the therapeutic arsenal for HF, since it provokes negative chronotropism by inhibiting sinoatrial node pacemaker activity through selectively blocking If current. However, it does not affect myocardial contractility, ventricular repolarization, or intracardiac conduction.¹

The SHIFT study showed that when ivabradine was added in patients with sinus rhythm, with HR $\geq$ 70 bpm, and LVEF $\leq$ 35%, who remained symptomatic despite normal drug treatment, it was associated with a reduction in the composite outcome of cardiovascular death or hospital admission for HF, but not with cardiovascular mortality or all causes mortality.³²

Pharmacokinetics

The initial dose recommended is 5 mg twice a day. In patients with regard to whom there are concerns that a reduction in HR could cause hemodynamic compromise or who have conduction defects, the initial dose can be 2.5 mg twice a day. The dose should be adjusted every 2 weeks with the objective of achieving an HR of 50-60 bpm up to a maximum dose of 7.5 mg twice a day.³³

Renal failure has a minimal impact on the pharmacokinetics of ivabradine, because it is primarily metabolized by cytochrome p450 (CYP3A4) in the liver and in the gastrointestinal tract.^{34,35} Plasma concentration peaks after approximately 1 h in fasting patients and food intake can delay this peak by 1 h. It has been demonstrated that mild liver failure can increase ivabradine levels by up to 20%³⁶ and the drug is contraindicated in severe liver failure.³²

Adverse effects

The side effects of ivabradine most commonly reported in clinical practice are bradycardia, AF, and phosphenes.³⁷ In the SHIFT study, 5% of the patients exhibited symptomatic bradycardia and the drug was associated with a small increase in the incidence of AF. Its use should therefore be reconsidered in patients who have paroxysmal AF.³² Although it is not considered that ivabradine prolongs the QT interval, it has been associated with torsade de pointes in experimental models and in combination with other medications³⁸⁻⁴¹ and caution should be exercised when it is used in conjunction with medications that prolong the QT interval. Ivabradine should not be taken during pregnancy.

Practical aspects:⁹

- Monitor heart rate, arterial blood pressure, and clinical status.
- Start with an initial dose of 5 mg 2x/day.
- The daily dose can be increased, reduced, or withdrawn depending on the patient's heart rate at rest. If resting heart rate is between 50 and 60 beats per minute, the current dose should be maintained.
- Titrate doses every 2 weeks, if possible, aiming for the target dose or the highest dose tolerated, on the basis of heart rate at rest.

- Treatment should be reduced or withdrawn if heart rate at rest remains persistently below 50 b.p.m. or if there are symptoms of bradycardia:

- Ivabradine should be withdrawn if a patient develops persistent/continuous AF during treatment with it.

- The visual phenomena are generally transitory and disappear during the first months of treatment with ivabradine and are not associated with severe retina dysfunction. However, withdrawal of ivabradine should be considered if they cause the patient discomfort.

- If symptoms occur in patients with intolerance to lactose or galactose (a component of the ivabradine tablet), it may be necessary to withdraw the medication.

Digoxin

The DIG study randomized 6800 patients with HFrEF to receive digoxin or placebo and showed that the drug did not reduce mortality, but did reduce hospital admissions for HF.⁴¹ Consequently, the guidelines recommend that digoxin be considered an adjunct to optimized therapy in symptomatic patients with HFrEF. If the patient has sinus rhythm, ivabradine should be preferred, but if there is AF, digoxin can be used alone,^{3,33} although there is considerable controversy about the safety of using digoxin in patients with AF.⁴³

Mechanism of action

Digoxin is a cardiac glycoside that belongs to the drug class digitalis glycosides. It has two mechanisms of action. Inhibition of the Na-K ATPase pump induces increased intracellular sodium, followed by a relative reduction in expulsion of calcium from the sarcomere, causing an increase in cardiac contractility. The other mechanism encompasses inhibition of the atrioventricular node (AVN). Elevation of the calcium levels leads to prolongation of phases 4 and 0 of the cardiac action potential, thereby increasing the refractory period of the AVN. The drug also stimulates the parasympathetic nervous system, reducing electrical conduction in the AVN and heart rate.^{1,44}

Pharmacokinetics

All of the cardiac glycosides are widely distributed through the tissues, including in the central nervous system (CNS). Almost two thirds of digoxin is excreted unaltered by the kidneys. Its renal clearance is proportional to creatinine clearance, with a half-life of 36 to 40 hours in patients with normal renal function.^{1,44} It is necessary to adjust the dose in the presence of renal function deficiency (Table 1). Corticosteroids and diuretics that cause potassium depletion increase the toxicity of digoxin.^{45,46}

Adverse effects

Digoxin toxicity is clinically relevant, because it can lead to fatal cardiac arrhythmias.⁴⁷ One clinical trial has suggested that serum levels exceeding 1.2 ng/mL are associated with increased risk of death in patients with AF.⁴⁸ However, toxicity can occur at lower levels in the presence of other risk factors, such as low body weight, advanced age, reduced renal function, and hypokalemia.^{49,50}

The incidence of side effects is estimated at up to 20%, around 50% of which are cardiac symptoms (such as arrhythmia and 1st degree AV block), 25% are gastrointestinal tract symptoms (anorexia, nausea, vomiting), and the remainder are CNS manifestations (headache, malaise, fatigue, disorientation) and other side effects. Digoxin is contraindicated in the following conditions: acute myocardial infarction, hypersensitivity to the drug, ventricular fibrillation, myocarditis, hypomagnesemia, hypokalemia, and Wolf-Parkinson-White syndrome.⁵⁰ Use of digoxin in pregnancy appears to be safe.³

Practical Aspects:¹⁰

- In patients taking Digoxin, serum potassium and creatinine should be measured whenever the digoxin dose is increased or drugs that could cause interactions are introduced, since there is a risk of toxicity with digoxin.

- Patients with impaired renal function, the elderly, those with low body weight, and women are at increased risk of digoxin toxicity and need more frequent monitoring.

- Routine digoxin level tests are unnecessary to assess toxicity and should not be used to guide long-term treatment.

Diuretics in heart failure

The majority of patients with Heart Failure with reduced Ejection Fraction (HFrEF) need a diuretic to control symptoms of congestion, particularly if they are acutely decompensated.⁵¹ (Chart 3) Loop diuretics (especially furosemide) are the preferred agents, although use of thiazide in patients with little response to increasing loop diuretic doses has been recommended in observational studies or small scale trials.⁵² The main adverse effects of diuretics are volume and/or electrolyte depletion and excessive diuresis can also predispose to hypotension and acute kidney damage. Some patients can benefit from a diuretic dosing regimen, by which they weigh themselves daily and dosage is adjusted if weight increases or reduces beyond a specific range.⁷

However, it is important to emphasize that these diuretics are symptomatic drugs, since no randomized clinical trials have demonstrated increased survival associated with their use in ambulatory patients with chronic HF.³ Additionally, observational studies have demonstrated potential harmful effects on the RAAS of chronic and continual use of diuretics,^{54,55} suggesting association with worse clinical outcomes. It is therefore recommended to always use the smallest therapeutic dose necessary with continual use of diuretics.⁵³ (Table 2)

Loop diuretics

Compared with all of the other classes of diuretics, these drugs exhibit the greatest efficacy for mobilization of Na⁺ and Cl⁻ in the body. They produce abundant quantities of urine, because they act on the thick ascending limb of Henle's loop, where the greatest resorption rate occurs, in comparison with other parts of the nephron. Furosemide is the most used drug in this group.^{2,17} Ethacrynic acid has a steeper dose-response curve than Furosemide, but is associated with more adverse effects than observed with other loop diuretics and so its use is limited. Bumetanide is much more potent than furosemide.

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Table 1 – Recommended Dosage

Recommended dose of digoxin according to GFR (ml/min/1.73m ²)	
GFR ml/min/1.73m ²	Dose mg/dia
>90	0.25
60 - 90	0.125
30 - 60	0.125 em dias alternados
<30	Do not use

Source: adapted from DiDomenico et al.⁵¹

Chart 3 – Recommendations from the Brazilian Heart Failure Guidelines – 2018³

Loop diuretics to control congestion. Class/Evidence level (EL): I/C
Thiazide diuretic combined with a loop diuretic to control persistent congestion, despite optimized treatment and increased loop diuretic dosages. Class/EL: I/B ⁵³
Initiate diuretics while HFrEF asymptomatic. Class/EL: III/C

HFrEF: heart failure with reduced ejection fraction.

Table 2 – Diuretics most frequently used in decompensated HF. Source: Heart Failure Guidelines Coordinating Committee, 2018

Medication	Route	Interval	Minimum dose	Maximum dose
Loop diuretic				
Furosemide	IV/PO	4/4h-6/6h Variable	20 mg 40 mg	240 mg 240mg
Bumetanide	IV	6/6h	0.5-2mg	10 mg
Thiazide				
Hydrochlorothiazide	PO	12/12h-24/24h	25 mg	100 mg
Chlorthalidone	PO	12/12h-24/24h	12.5mg	50 mg
Indapamide	PO	24/24h	mg	5 mg

IV: intravenous; PO: by mouth.

Mechanism of action

These drugs inhibit activity of the Na⁺-K⁺-2Cl⁻ cotransporter in the thick ascending limb of Henle's loop, which is why they are called loop diuretics. This is the most effective mechanism for provoking diuresis and is responsible for resorption of 25 to 30% of filtered NaCl. For example, although the DCT reabsorbs around 65% of filtered Na⁺, the diuretics that only act on this tubule have limited efficacy because the thick ascending limb reabsorbs a large proportion of the rejected material. Additionally, those that predominantly act on sites after the thick ascending limb (such as the Convolutated Distal Tubule and the Collector Tubule) have limited efficacy, because only a small percentage of the filtered Na⁺ reaches these more distal sites.^{2,17}

Pharmacokinetics

Approximately 65% of Furosemide is excreted unaltered in urine and the remainder is conjugated with glucuronic acid in the kidneys. Thus, the half-life of furosemide clearance is

prolonged in patients with kidney disease who are free from liver disease. In contrast, bumetanide and torsemide exhibit significant hepatic metabolism, so that their half-lives can be extended in the presence of liver disease.^{2,17,56} (Table 3)

The mean oral availability of furosemide is approximately 60% and the natriuretic response is rapid, with peak activity at 20 to 30 minutes and duration of 4 to 6 hours.⁵⁷ Torsemide and Bumetanide have similar half-life and duration relatively, but they are more powerful and have greater bioavailability (from 60 to 80%).⁵⁸

As a class, loop diuretics have short clearance half-lives and are not available in slow-release preparations. As a result, intervals between administration must be short to maintain them at adequate concentrations within the tubule lumen.⁷

Adverse effects

Loop diuretics act rapidly and provoke changes in the composition of urine and increase the volume excreted. In

relation to electrolytes, these drugs considerably deplete Na^+ , Ca^{+2} , and K^+ and can also deplete Mg^{+2} , especially in the elderly. Particularly in the case of hyponatremia, the consequence of less Na^+ arriving at the DCT and collector tubule can, in the final analysis, trigger hypochloremic and hypokalemic metabolic alkalosis.⁵⁷

Additionally, another classic adverse effect associated with this class of drugs is ototoxicity (in general reversible). This emerges as a buzzing, compromising hearing, with deafness, vertigo/dizziness, and feelings of blocked ears. It is commonly more related to cases of intravenous administration of this drug class or in cases of combinations with other medications capable of provoking this, such as aminoglycosides.^{2,17}

It is worth noting that loop diuretics can also interfere in homeostasis of other metabolites. For example, uric acid (with hyperuricemia, and in some cases it can provoke gout), glucose (with hyperglycemia), and cholesterol (with increased plasma levels, especially of LDL).^{2,56}

People with hypersensitivity to sulfonamides have a contraindication to taking loop diuretics derived from them. Additionally, some medications can interfere with their efficacy, such as the non-steroidal anti-inflammatory drugs (NSAIDs).²

Thiazide

Mechanism of action

Thiazide derivatives increase diuresis, primarily acting on the DCT, reducing resorption of Na^+ by inhibition of the Na^+/Cl^- cotransporter in the luminal membrane of tubules.^{2,17,56}

This increase in urinary output also causes increased urinary excretion of some other elements, including K^+ and Mg^{+2} , especially in the elderly. The cause of hypokalemia is the fact that inhibitors of the Na^+/Cl^- cotransporter provoke a filtrate with higher Na^+ concentration and consequently increase urinary excretion of K^+ because of the exchange mechanism that occurs in the collector tubule (discussed in the section on mineralocorticoid antagonists). In turn, hypomagnesemia is an effect that is particularly seen in the elderly because administration of these drugs can cause magnesuria, through a little-understood mechanism.¹⁷

In relation to electrolytes that are spared, excretion of Ca^{+2} is reduced because chronic administration of thiazide provokes volume depletion, which requires more intense proximal resorption, but also because the class has the effect of increasing resorption of this cation in the DCT.

Pharmacokinetics

It is important to emphasize that the pharmacokinetics of thiazide diuretics can be very variable, depending on the drug in question (Table 4), but in general, the maximum excretion of Na^+ load is just 5%, because around 90% of the Na^+ load filtered is reabsorbed before reaching the DCT. Hydrochlorothiazide is one of the main members of this class, with intestinal absorption of 65%, plasmatic protein binding of 40%, and clearance half-life of approximately 10 hours, with 95% of the dose eliminated unaltered via urine. The duration of hydrochlorothiazide activity is 18-24 hours. Intestinal absorption of this drug may be reduced in patients with heart failure. The natriuretic action of thiazide reduces rapidly when glomerular filtration is less than 30 ml/minute and these

Table 3 – $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter inhibitors (loop diuretics)

Drug	Relative Potency	Oral availability	Half-life (hours)	Excretion pathway
Furosemide	1	~60%	~1.5h	~65%R ~35%M ^a
Bumetanide	40	~80%	~0.8h	~62%R ~38%M

^a For furosemide, metabolism is primarily in the kidneys. R: renal excretion of the intact drug; M: metabolism.

Table 4 – Na^+/Cl^- cotransporter inhibitors (thiazide and similar)

Drug	Relative Potency	Oral availability	Half-life (hours)	Excretion pathway
Hydrochlorothiazide	1	~70%	~2.5h	R
Chlorthalidone	1	~65%	~47h	~65%R ~10%B ~25%U
Indapamide	20	~93%	~14h	M

R: renal excretion of the intact drug; M: metabolism; B: excretion of the intact drug in the bile; U: excretion pathway unknown.

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drugs become ineffective when glomerular filtration is less than 10ml/minute.^{2,17,58}

Adverse effects

The most severe adverse effects of thiazides are related to abnormalities of fluid and electrolyte balance. These adverse effects include depletion of extracellular volume, hypotension, hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, and hypomagnesemia.⁵⁶ These diuretics have also shown the potential to interfere in metabolism of other compounds, explaining the emergence of hyperuricemia, hyperglycemia, and hyperlipemia.^{2,17}

Hypokalemia may be related to reduction in insulin secretion, which would explain the changes to glucose metabolism, such as increased tolerance. Control of diabetes may therefore be compromised during treatment. Additionally, thiazides can cause increases of 5 to 15% in serum cholesterol concentration and also increases in serum low density lipoproteins.^{2,17}

Rarely, thiazide diuretics can provoke disorders of the central nervous system (for example: vertigo/dizziness, paresthesias, xanthopsia, and weakness) and the gastrointestinal tract (for example: anorexia, nausea, vomiting, cramps, diarrhea, constipation, cholecystitis, and pancreatitis), hematological disorders (for example: blood dyscrasia) and dermatological disorders (for example: photosensitivity and exanthemas).²

Thiazide diuretics are contraindicated for people hypersensitive to sulfonamides. In relation to drug interactions, they can reduce the effects of anticoagulants, uricosuric agents used to treat gout, sulfonylureas, and insulin and can increase the effects of anesthetics, diazoxide, glycosides, digitalis glycosides, lithium, loop diuretics, and vitamin D.

The effectiveness of thiazide diuretics can be reduced by NSAIDs and non-selective or selective COX-2 inhibitors. Amphotericin B and corticosteroids increase the risk of hypokalemia induced by these diuretics. A potentially lethal drug interaction occurs between thiazide diuretics and quinidine, because the QT interval prolongation caused by quinidine can lead to development of torsade de pointes (a polymorphic ventricular tachycardia).²

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Practical aspects (loop diuretics and thiazide)

- Test renal function and electrolytes, particularly in patients on combined use of loop diuretics and thiazide.
- Start with a low dose, but adjust to an effective dose to achieve satisfactory diuresis, with reduction of body weight of 0.75 to 1.0 Kg/day.⁹
- Dose adjustment should be according to symptoms and/or signs of congestion, arterial blood pressure, and renal function, always targeting the smallest dose possible to maintain euvolemia – the patient's "dry weight".⁹
- Remember that excessive diuresis is more dangerous than edema, primarily because of the risk of hypovolemia and hypokalemia.⁹
- Monitor serum levels of Urea, Creatinine and K⁺ between 1 and 2 weeks after initiation and after any increase in dosage.⁹

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