Heart Failure

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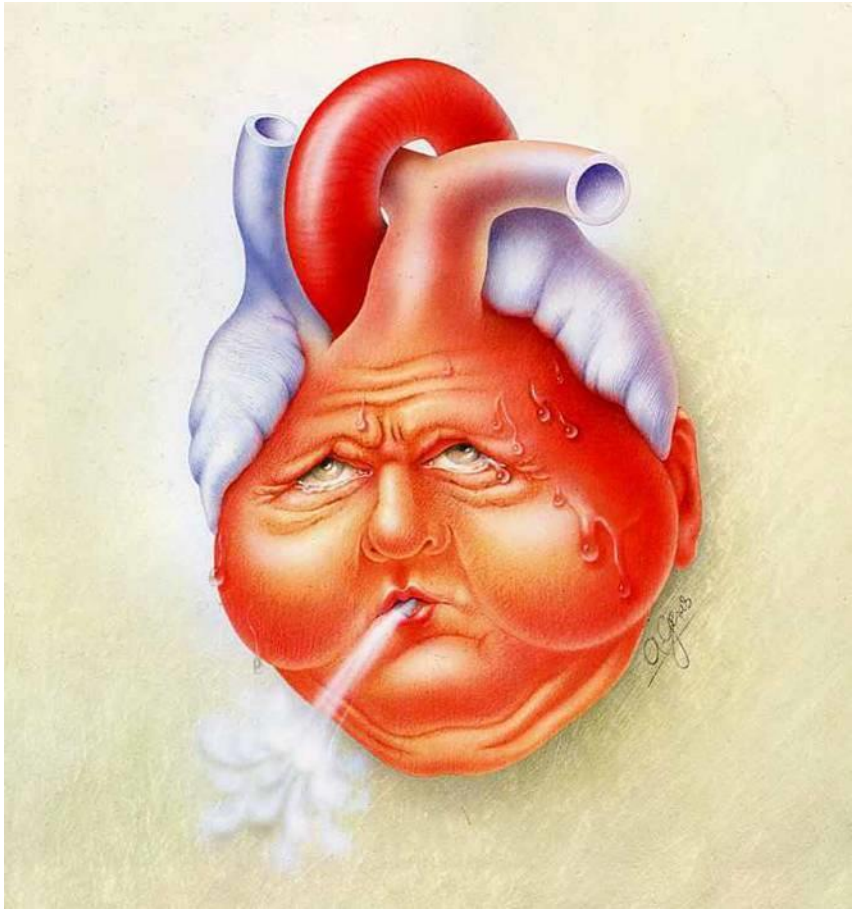

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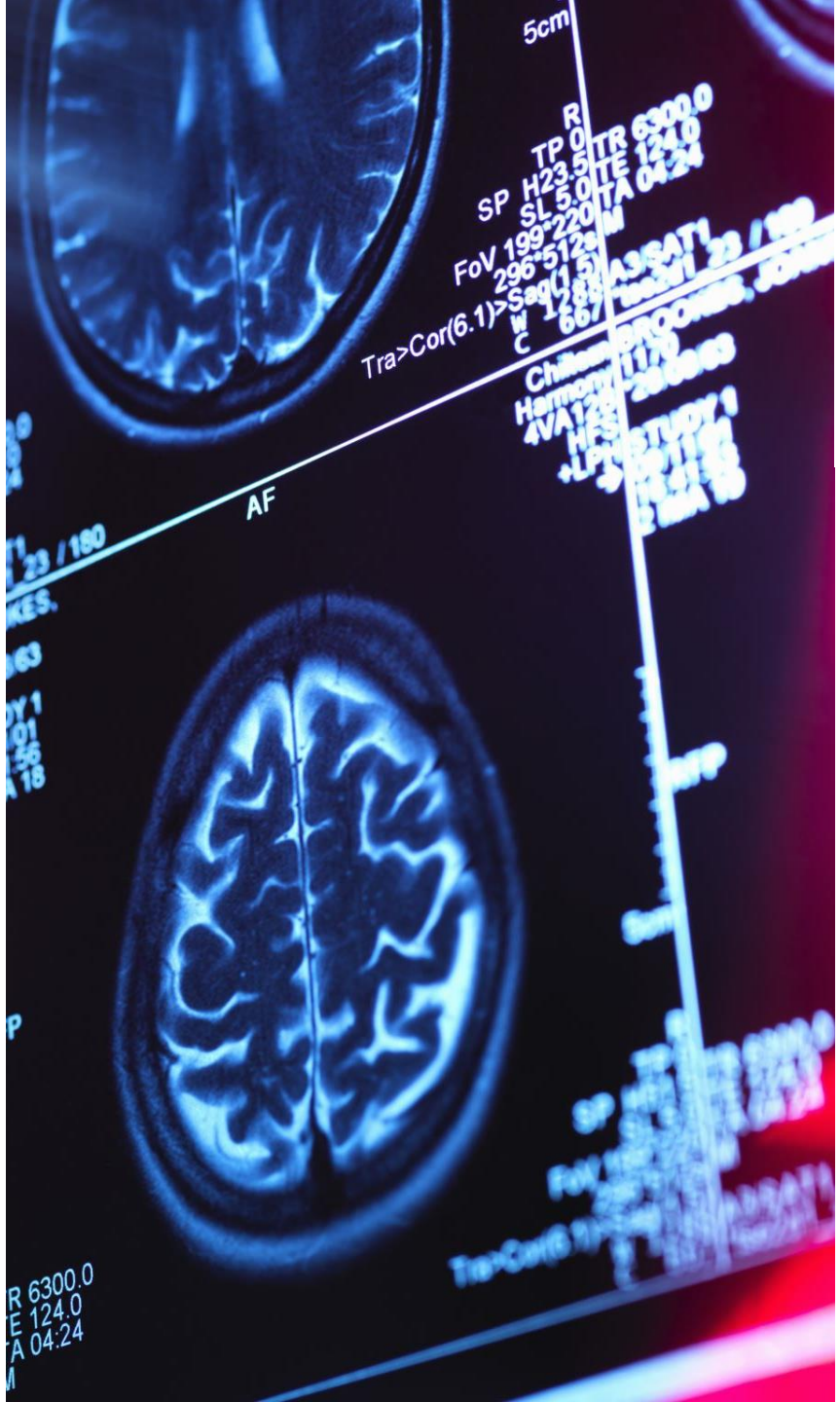
- **I. OVERVIEW**
  Heart failure (HF) **is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.**
- ***Its cardinal symptoms are dyspnea, fatigue, and fluid retention.***
- HF is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid (hence the term "**congestive" HF,** because symptoms include dyspnea from ***pulmonary congestion in left HF and peripheral edema in right HF).***
- Underlying **causes of HF** include *1. arteriosclerotic heart disease, 2.myocardial infarction, 3. hypertensive heart disease, 4.valvular heart disease, 5.dilated cardiomyopathy, and 6. congenital heart disease. 7. Left systolic dysfunction secondary to coronary artery disease* is the most common cause of HF, accounting for nearly 70 percent of all cases.



- **A. Role of physiologic compensatory mechanisms in the progression of HF**
  Chronic activation of the sympathetic nervous system and the renin angiotensin-aldosterone axis is associated with ***remodeling of cardiac tissue***, ***characterized by loss of myocytes, hypertrophy, and fibrosis.***
  The geometry of the heart becomes less elliptical and more spherical, interfering with its ability to efficiently function as a pump. This prompts additional neuro humoral activation, creating a vicious cycle that, if left untreated, leads to death.

- **B. Goals of pharmacologic intervention in HF**
  The goals are to **alleviate symptoms, slow disease progression, and improve survival**.
- Accordingly, ***six classes of drugs*** have been shown to be effective: **1) inhibitors of the renin-angiotensin system, 2) β-adrenoreceptor blockers, 3) diuretics, 4) direct vasodilators, 5) inotropic agents, and 6) aldosterone antagonists** (Figure 16.1). Depending on the severity of cardiac failure and individual patient factors, one or more of these classes of drugs are administered. Beneficial effects of pharmacologic intervention include **reduction of the load on the myocardium, decreased extracellular fluid volume, improved cardiac contractility, and slowing the rate of cardiac remodeling.**
- Knowledge of the physiology of cardiac muscle contraction is essential to understanding the compensatory responses evoked by the failing heart as well as the actions of drugs used to treat HF

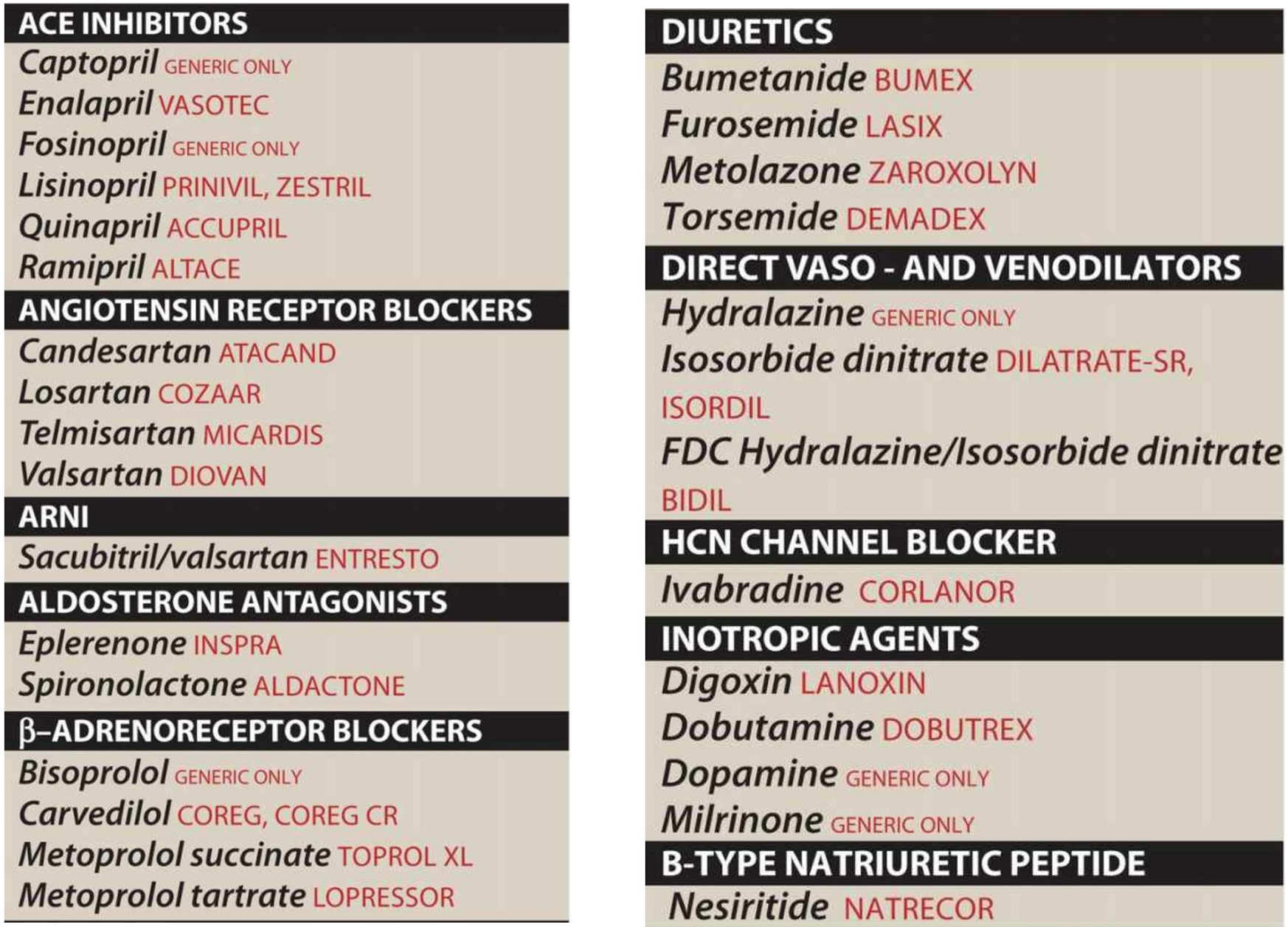
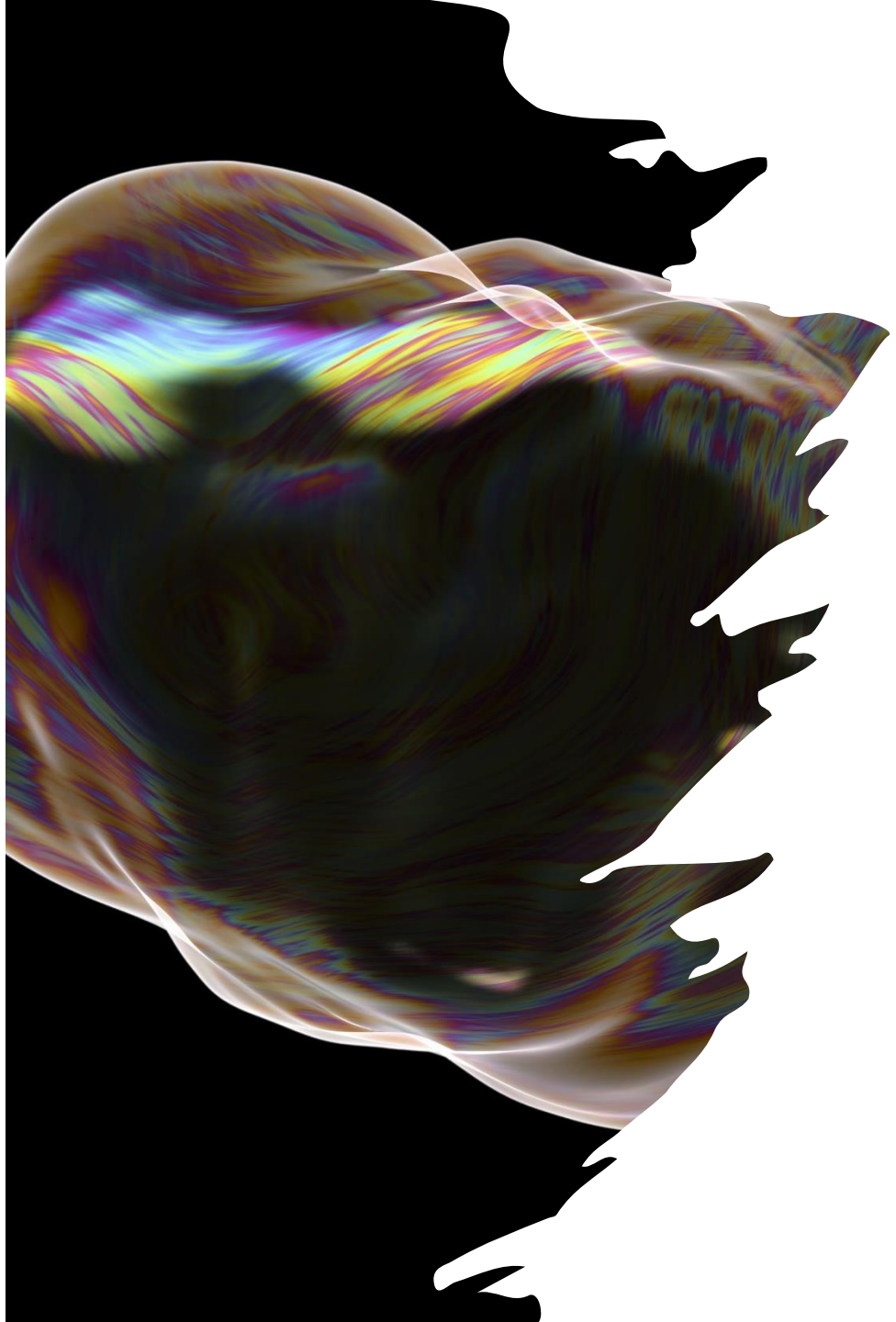

ACE INHIBITORS
Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE
ANGIOTENSIN RECEPTOR BLOCKERS
Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN
ARNI
Sacubitril/valsartan ENTRESTO
ALDOSTERONE ANTAGONISTS
Eplerenone INSPRA
Spironolactone ALDACTONE
β–ADRENORECEPTOR BLOCKERS
Bisoprolol GENERIC ONLY
Carvedilol COREG, COREG CR
Metoprolol succinate TOPROL XL
Metoprolol tartrate LOPRESSOR
DIURETICS
Bumetanide BUMEX
Furosemide LASIX
Metolazone ZAROXOLYN
Torsemide DEMADEX
DIRECT VASO - AND VENODILATORS
Hydralazine GENERIC ONLY
Isosorbide dinitrate DILATRATE-SR, ISORDIL
FDC Hydralazine/Isosorbide dinitrate BIDIL
HCN CHANNEL BLOCKER
Ivabradine CORLANOR
INOTROPIC AGENTS
Digoxin LANOXIN
Dobutamine DOBUTREX
Dopamine GENERIC ONLY
Milrinone GENERIC ONLY
B-TYPE NATRIURETIC PEPTIDE
Nesiritide NATRECOR

Figure 16.1



- **II. PHYSIOLOGY OF MUSCLE CONTRACTION**
  The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the
  contractile proteins and ends with relaxation and return to the resting state.
  However, unlike skeletal muscle, which shows graded contractions depending on the number of muscle cells that are stimulated, the cardiac muscle cells are interconnected in groups that respond to stimuli as a **unit**, contracting together whenever a single cell is stimulated.

- **A. Action potential**

Cardiac muscle cells are electrically excitable. However, unlike the cells of other muscles and nerves, the cells of cardiac muscle show a ***spontaneous, intrinsic rhythm*** generated by specialized “pacemaker” cells located in the sinoatrial and atrioventricular (AV) nodes.

The cardiac cells also have an unusually ***long action potential***, which can be divided into ***five phases (0–4).*** Figure 16.2 illustrates the major ions contributing to depolarization and polarization of cardiac cells.

These ions pass through channels in the sarcolemmal membrane and, thus, create a current.

The channels open and close at different times during the action potential.
Some respond primarily to changes in ion concentration, whereas others are sensitive to adenosine triphosphate or to membrane voltage

- **B. Cardiac contraction**
  The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase these calcium levels (or that increase the sensitivity of the contractile machinery to calcium).
- increase the force of contraction **(inotropic effect**). [Note: The inotropic agents increase the contractility of the heart by directly or indirectly altering the mechanisms that control the concentration of intracellular calcium.]

- **1. Sources of free intracellular calcium:** Calcium comes from several sources. The **first** is from **outside the cell**, where opening of voltage sensitive calcium channels causes an immediate rise in free cytosolic calcium. **Calcium may also enter by exchange with sodium**. Calcium is also **released from the sarcoplasmic reticulum and mitochondria**, which further increases the cytosolic level of calcium (Figure 16.3).

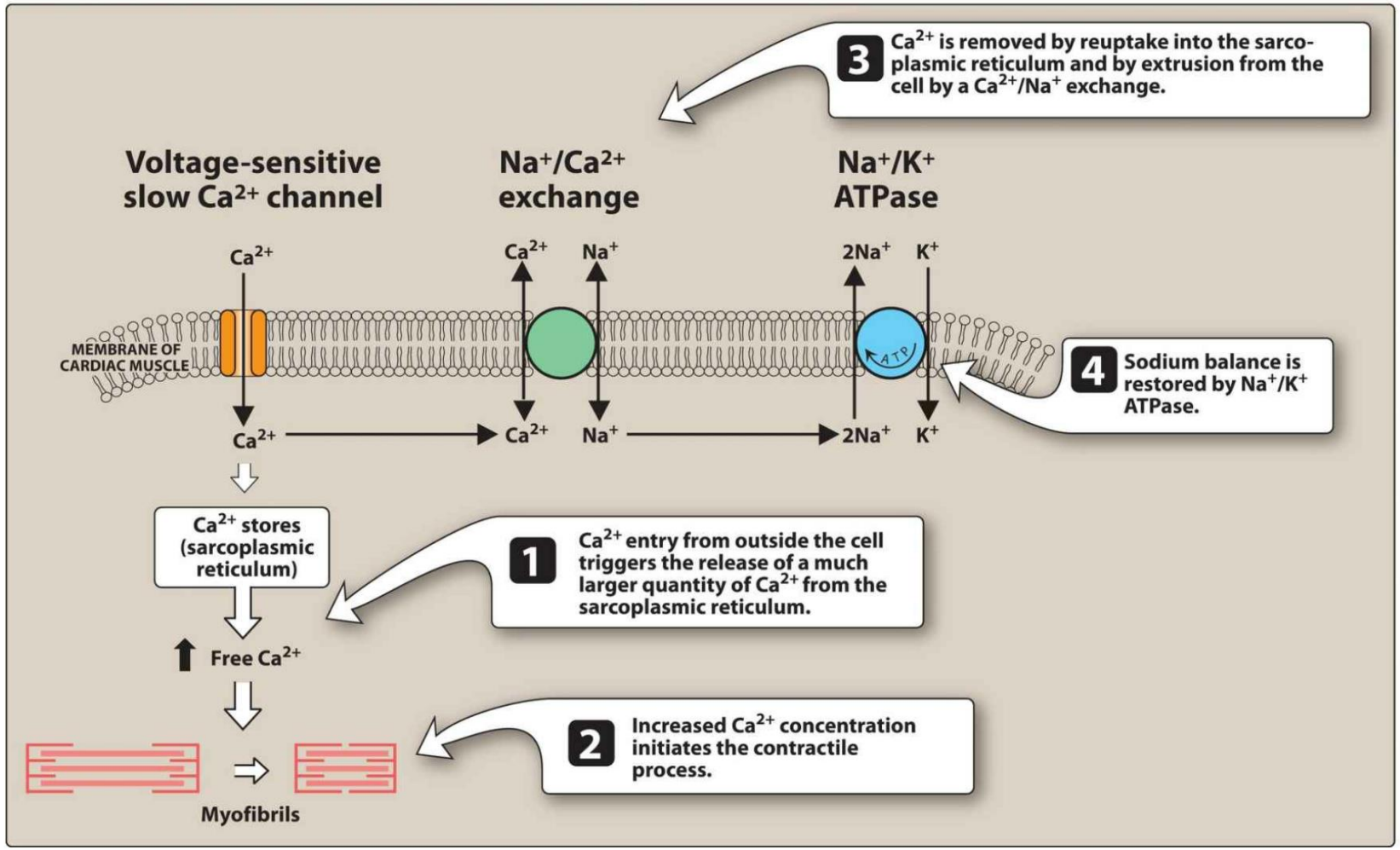


Figure 18.3 Ion movements during the contraction of cardiac muscle. ATPase = adenosine triphosphatase.

2. Removal of free cytosolic calcium: If free cytosolic calcium levels were to remain high, the cardiac muscle would be in a constant state of contraction rather than showing a periodic contraction. Mechanisms of removal include the following two alternatives.

A. **Sodium/calcium exchange:** Calcium is removed by a sodium/ calcium exchange reaction that reversibly exchanges calcium ions for sodium ions across the cell membrane (see Figure 16.3).

b. Uptake of calcium by the sarcoplasmic reticulum and mitochondria: Calcium is also recaptured by the sarcoplasmic reticulum and the mitochondria. More than 99 percent of the intracellular calcium is located in these organelles, and even a modest shift between these stores and free calcium can lead to large changes in the concentration of free cytosolic calcium.

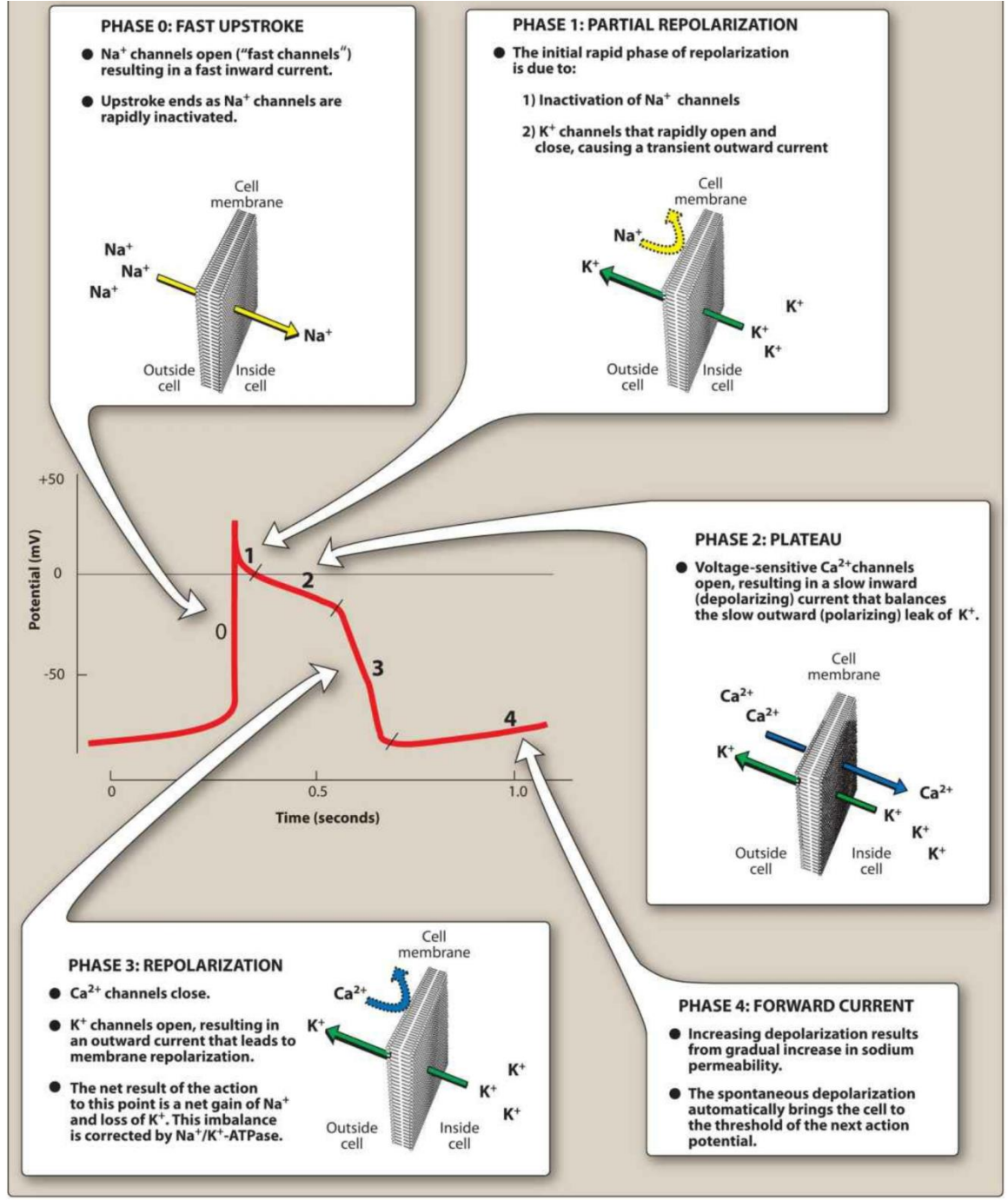


Figure 18.2 Action potential of a cardiac myocyte. ATPase = adenosine triphosphatase.

- **C. Compensatory physiological responses in HF**
  The failing heart evokes ***four major compensatory mechanisms*** to enhance cardiac output (Figure 18.4).
- **1. Increased sympathetic activity**
  Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system. In an attempt to sustain tissue perfusion, this stimulation of β-adrenergic receptors results in ***an increased heart rate and a greater force of contraction of the heart muscle***. In addition, vasoconstriction enhances venous return and increases cardiac preload. An increase in preload (stretch on the heart) increases stroke volume, which, in turn, increases cardiac output.
- These compensatory responses increase the workload of the heart, which, in the long term, contributes to further decline in cardiac function.

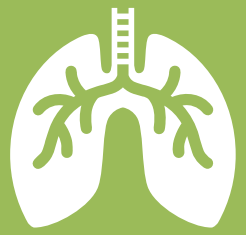
- **2. Activation of the renin-angiotensin system:**

A fall in cardiac output decreases blood flow to the kidney, prompting the release of **renin**, with the resulting increase in the formation of **angiotensin II** and release of **aldosterone**. This results in increased peripheral resistance and retention of sodium and water.

Blood volume increases, and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases, and peripheral edema and pulmonary edema occur (see Figure 16.4). These **compensatory responses increase the work of the heart** and, therefore, can contribute to further decline in cardiac function.

- **3. Activation of natriuretic peptides**
  An increase in preload also increases the release of natriuretic peptides. Natriuretic peptides, which include **atrial, B type, and C-type**, have differing roles in HF; atrial and B-type natriuretic peptides are the most important. Activation of the natriuretic peptides ultimately results in **vasodilation**, natriuresis, inhibition of renin and aldosterone release,
  and a reduction in myocardial fibrosis. This beneficial response may improve cardiac function and HF symptoms.
  4. Myocardial hypertrophy
  Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contractions and a diminished ability to eject blood. This type of failure is termed "**systolic failure**" or **HF with reduced ejection fraction (HFrEF)** and is the result of the ventricle being unable to
  pump effectively.

Patients with HF may have "**diastolic dysfunction**," a **term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy.**



The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed "**diastolic HF" or HF with preserved ejection fraction (HFpEF).**

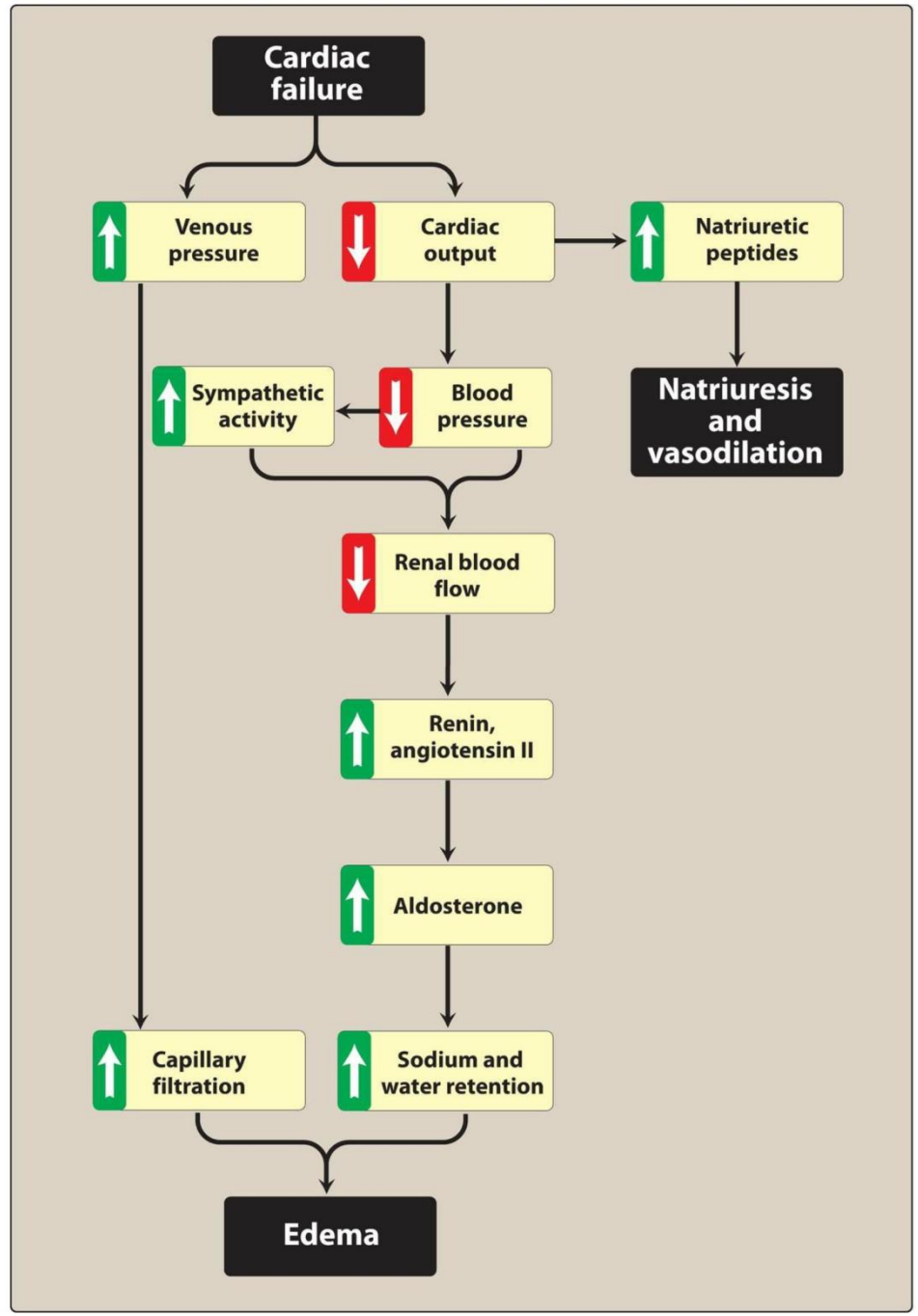


Figure 18.4 Cardiovascular consequences of HF.

- **D. Acute (decompensated) HF**

If the compensatory mechanisms adequately restore cardiac output, HF is said to be compensated. If the compensatory mechanisms fail to maintain cardiac output, HF is decompensated and the patient develops worsening HF signs and symptoms. ***Typical HF signs and symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.***

- **E. Therapeutic strategies in HF**
- Chronic HF is typically managed by ***fluid limitations (less than 1.5 to 2 L daily); low dietary intake of sodium (less than 2000 mg/d); treatment of comorbid conditions; and judicious use of diuretics***.
- Specifically for HFrEF, inhibitors of the RAAS, inhibitors of the sympathetic nervous system, and drugs that enhance activity of natriuretic peptides have been shown to improve survival and reduce symptoms.
- **Inotropic agents are reserved for acute signs** and symptoms of HF and are used mostly in the inpatient setting. Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, non dihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

- **III. Inhibitors of the Renin–Angiotensin–Aldosterone System**
  The compensatory activation of the RAAS in HF leads to increased workload on the heart and a resultant decline in cardiac function. Therefore, inhibition of the RAAS is an important pharmacological target in the management of HF.
- **A. Angiotensin-converting enzyme inhibitors**
  Angiotensin-converting enzyme (ACE) inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. They also diminish the inactivation of bradykinin (Figure 18.5).

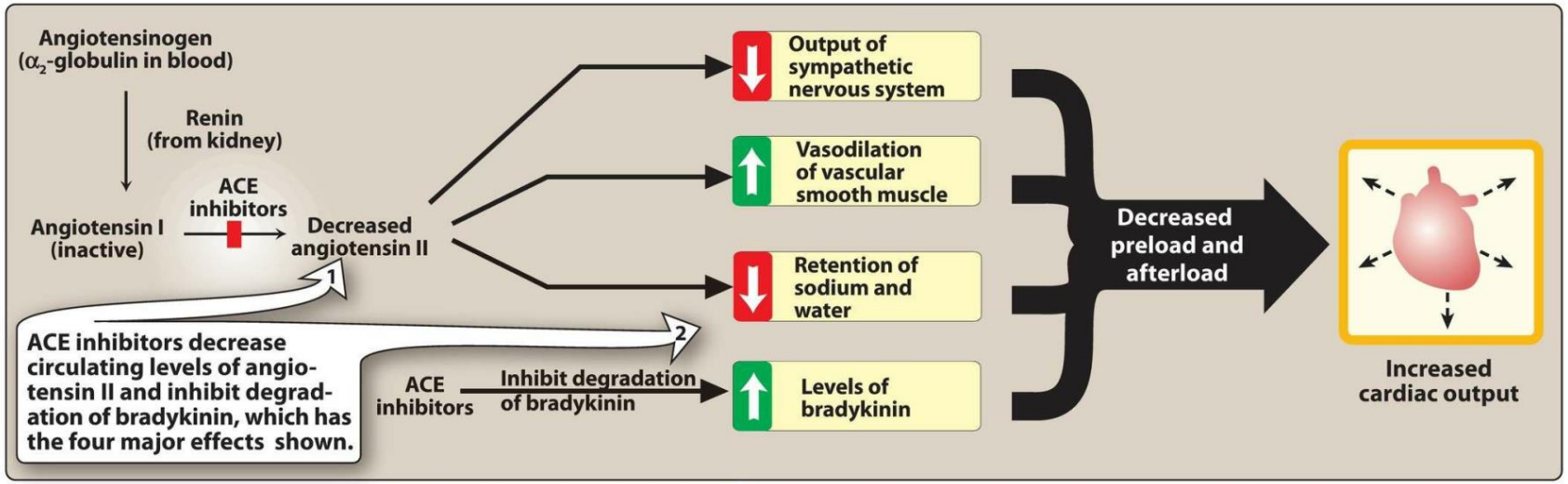


Figure 18.5 Effects of ACE inhibitors. [Note: The reduced retention of sodium and water results from two causes: decreased production of angiotensin II and aldosterone.]

1. **Actions**

   ACE inhibitors ***decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output.*** ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF.

ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.

- **2. Therapeutic use**
  ACE inhibitors may be considered for patients with ***asymptomatic and symptomatic HFrEF***. Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure. These agents should be started at low doses and titrated to target or maximally tolerated doses in the management of HFrEF.
- ACE inhibitors are also used in the treatment of hypertension (see Chapter 16). Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy.
- **3. Pharmacokinetics**
  ACE inhibitors are adequately absorbed following oral administration. Food may decrease the absorption of *captopril* [KAP-toe-pril], so it should be taken on an empty stomach. Except for *captopril* and injectable *enalaprilat* [en-AL-a-pril-at], ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors except *fosinopril* [foe-SIN-oh-pril], which also undergoes excretion in the feces. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer.

4. Adverse effects
see antihypertension chapter.

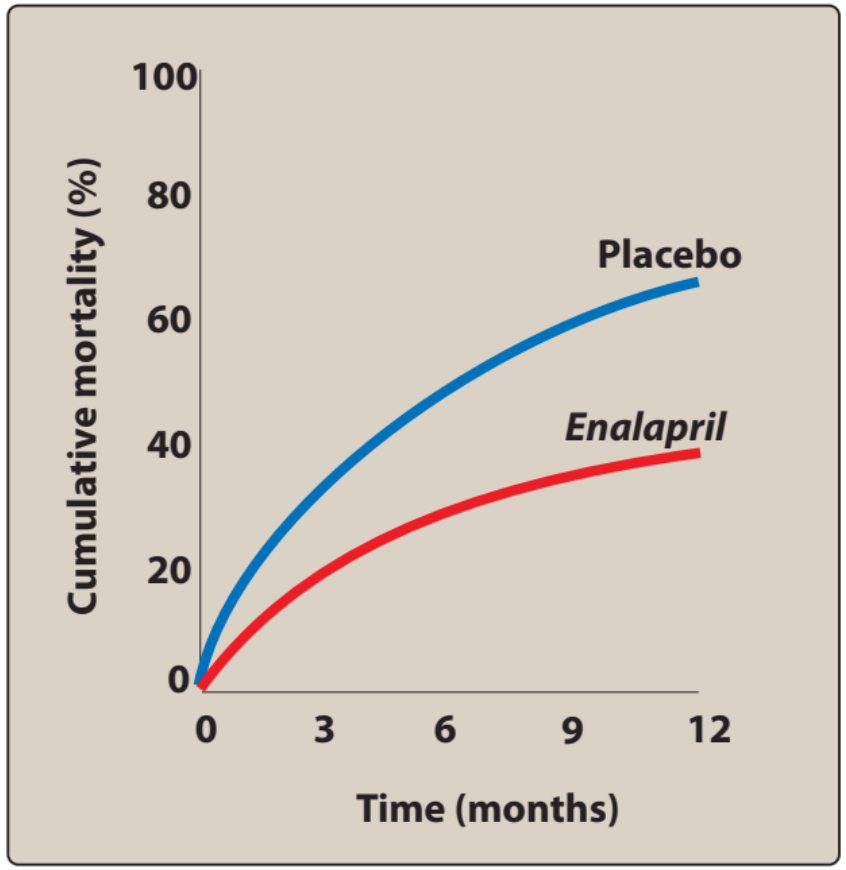


Figure 16.6
Effect of *enalapril* on the mortality of patients with congestive heart failure.

- **B. Angiotensin receptor blockers**
  1. Actions
  Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema, which are thought to be mediated by elevated bradykinin levels. ARBs are also used in the treatment of hypertension (see Chapter 16).
- **2. Pharmacokinetics**
  ARBs are orally active and are dosed once daily, with the exception of *valsartan* [val-SAR-tan], which is dosed twice daily. They are highly plasma protein bound. *Losartan* [loe-SAR-tan] differs in that it undergoes extensive
  first-pass hepatic metabolism, including conversion to an active metabolite. The other drugs have inactive metabolites. Elimination of metabolites and parent compounds occurs in urine and feces.

- **C. Aldosterone receptor antagonists**
  Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. ***Spironolactone*** [spir-ON-oh-LAK-tone] and ***eplerenone*** [ep-LER-e-none] *are antagonists of aldosterone at the mineralocorticoid receptor, thereby* ***preventing salt retention, myocardial hypertrophy, and hypokalemia*****.** *Spironolactone* also has affinity for androgen and progesterone receptors, and is associated with endocrine-related adverse effects such as gynecomastia and dysmenorrhea. Aldosterone antagonists are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction. Please see Chapter 17 for a full discussion of aldosterone receptor antagonists

- **IV. β-Blockers**
  Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, ***evidence clearly demonstrates improved systolic function and reverse cardiac remodeling in patients receiving β-blockers.***
- These benefits arise in spite of an occasional, initial exacerbation of symptoms. The benefit of β-blockers is attributed, in part, to their ***ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system***. *These agents decrease heart rate and inhibit release of renin in the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.* Three β-blockers have shown benefit in HFrEF: ***bisoprolol*** [bis-oh-PROE-lol], ***carvedilol*** [KAR-ve-dil-ol], and long-acting ***metoprolol*** *succinate* [me-TOE-proe-lol SUK-si-nate].

- β-Blockade is ***recommended for all patients with chronic, stable HFrEF.*** *Bisoprolol*, *carvedilol*, and *metoprolol succinate reduce morbidity and mortality associated with HFrEF.* Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs. Both *carvedilol* and *metoprolol* are metabolized by the cytochrome P450 2D6 isoenzyme, and inhibitors of this metabolic pathway may increase levels of these drugs and increase the risk of adverse effects. In addition, *carvedilol* is a substrate of P-glycoprotein (P-gp). Increased effects of *carvedilol* may occur if it is coadministered with P-gp inhibitors. β-Blockers should also be used with caution with other drugs that slow AV conduction, such as *amiodarone*, *verapamil*, and *diltiazem*.

- **V. Diuretics**
  Diuretics ***reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload).***
- This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure. **Loop diuretics** are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency. Since diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess. Please see Chapter 17 for a full discussion of diuretics.

- **VI. Angiotensin Receptor–Neprilysin Inhibitor**
  Neprilysin is the enzyme responsible for breaking down **vasoactive peptides bradykinin**, and **natriuretic peptides**. Inhibition of neprilysin augments the activity of the vasoactive peptides. To maximize the effect of natriuretic peptides, stimulation of the RAAS must be offset without further increase in bradykinin. Therefore an ARB, instead of an ACE inhibitor, is combined with a neprilysin inhibitor to reduce the incidence of angioedema (Figure 18.6).

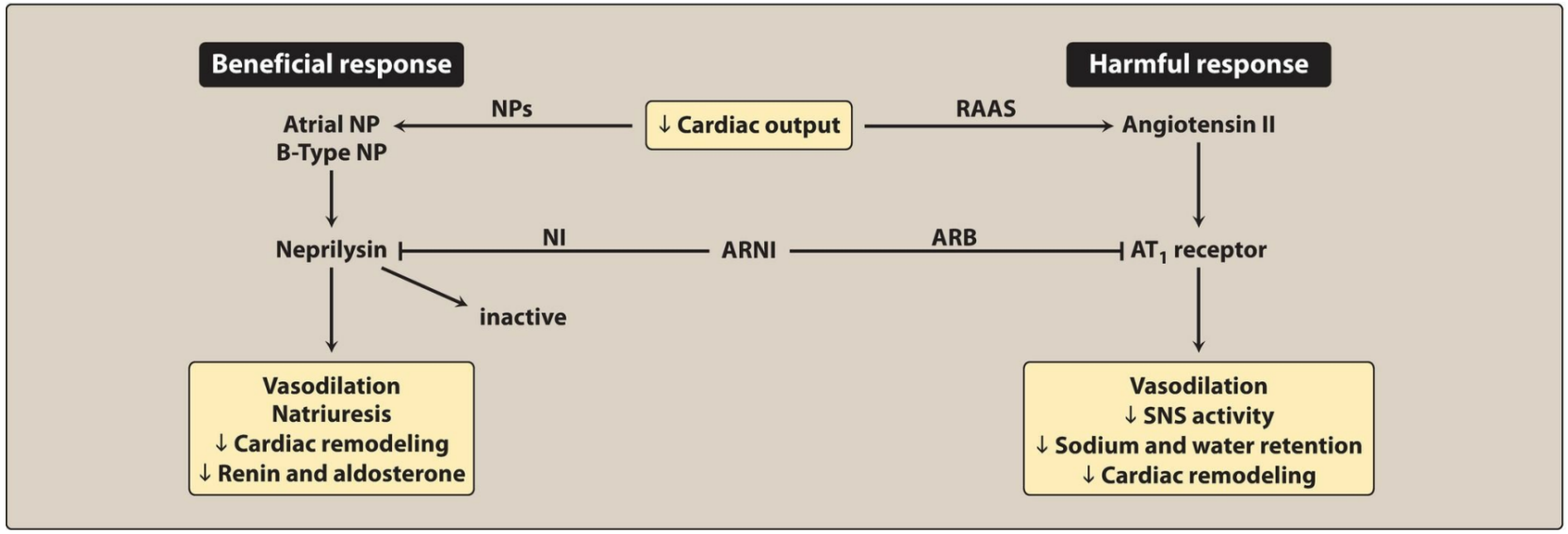


Figure 18.6 Effects of angiotensin receptor blocker–neprilysin inhibitors. ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; AT1 = angiotensin type 1; NI, neprilysin inhibitor; NP = natriuretic peptide; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system.

Entresto™

(sacubitril/valsartan) tablets

24/26mg · 49/51mg · 97/103mg

- **A. Sacubitril/valsartan (ENTRESTO)**
  Sacubitril [sak-UE-bi-tril]/*valsartan* is the first available angiotensin receptor–neprilysin inhibitor (ARNI).
  1. Actions
  Sacubitril/*valsartan* combines the actions of an ARB with neprilysin inhibition. Inhibition of neprilysin results in increased concentration of vasoactive peptides, leading to natriuresis, diuresis, vasodilation, and inhibition of fibrosis. Together, the combination decreases afterload, preload, and myocardial fibrosis. An ARNI improves survival and clinical signs and symptoms of HF, as compared to therapy with an ACE inhibitor.
  2. Therapeutic use
  An ARNI should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a β-blocker and an ACE inhibitor or ARB.

- **3. Pharmacokinetics**
  Sacubitril/*valsartan* is orally active, administered with or without food, and quickly breaks down into the separate components.
- *Sacubitril* is transformed to active drug by plasma esterases. Both drugs have a high volume of distribution and are highly bound to plasma proteins. *Sacubitril* is mainly excreted in the urine. The half-life of approximately 10 hours for both components allows for twice-daily dosing.

  4. Adverse effects

  The adverse effect profile is similar to that of an ACE inhibitor or ARB. Because of the added reduction of afterload, hypotension is more common with an ARNI. Due to inhibition of neprilysin with *sacubitril*, bradykinin levels may increase and angioedema may occur. Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angioedema associated with an ACE inhibitor or ARB. To minimize risk of angioedema, an ACE inhibitor must be stopped at least 36 hours prior to starting *sacubitril/valsartan*.

- **VII. Hyperpolarization-Activated Cyclic Nucleotide–Gated Channel Blocker**
  The hyperpolarization-activated cyclic nucleotide–gated (HCN) channel is responsible for the *If* current and setting the pace within the SA node. Inhibition of the HCN channel results in slowing of depolarization and a lower heart rate (Figure 18.7). Reduction in heart rate is use and dose dependent.

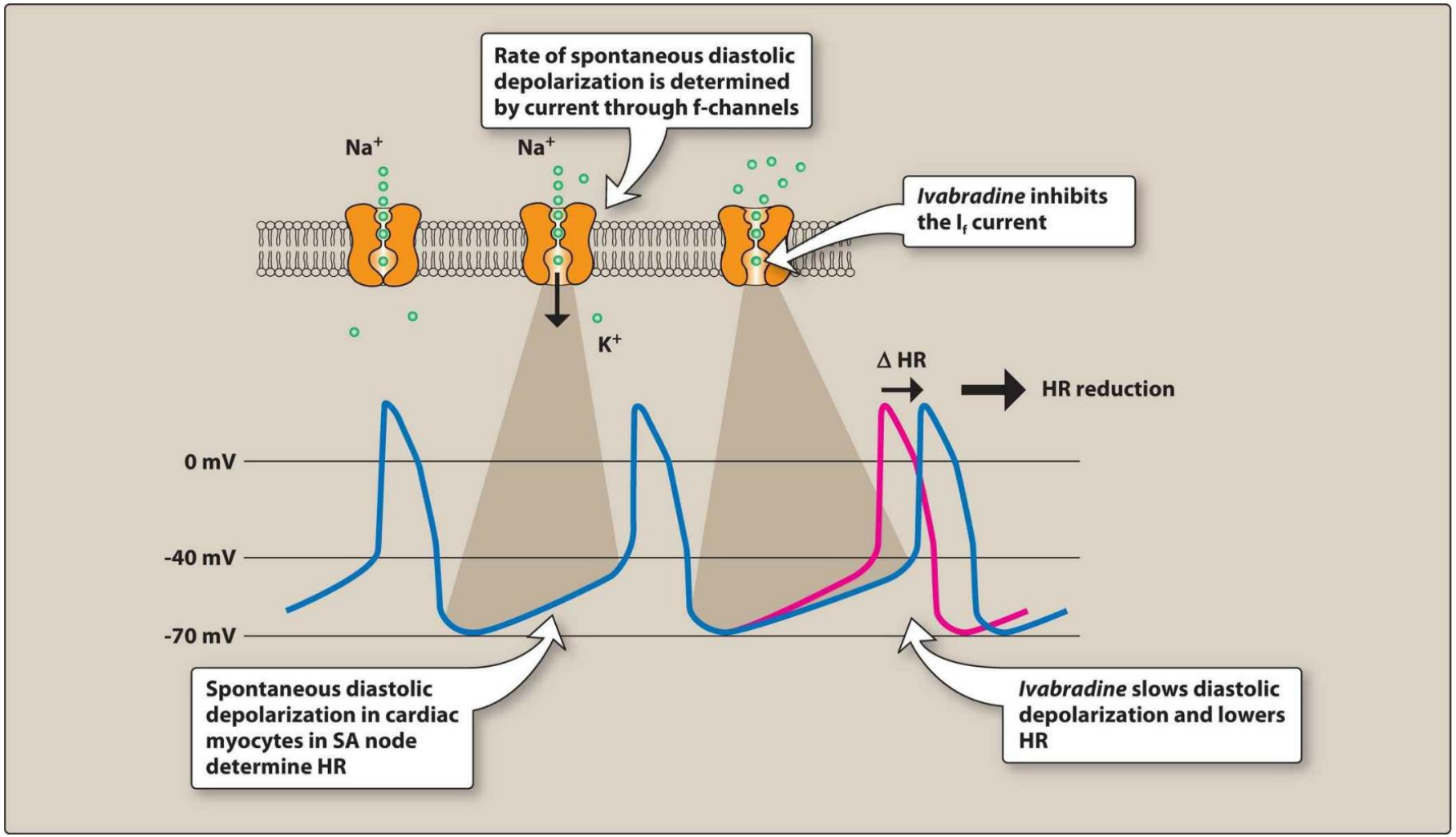


Figure 18.7 Effects of inhibition of I_f current with *ivabradine*. HR = heart rate; K^+ = potassium; Na^+ = sodium; SA = sinoatrial.


Procoralan 75
Procoralan 5mg
56 film-coated tablets
Oral route


AMGEN
NDC 55513-800-60
Corlanor
(ivabradine) tablets
5 mg
Each tablet contains 5 mg ivabradine equivalent to 5.39 mg ivabradine as hydrochloride.
Oral Use.
Store at 25°C, excursions permitted to 15°C - 30°C.
Keep out of the sight and reach of children.
℞ Only
60 Film-coated tablets
1017780
Manufactured by Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Made in Italy
Usual Dose: See package insert for dosage
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Patent: http://pat.amgen.com/corlanor/

- **A. Ivabradine**
  Ivabradine [eye-VAB-ra-deen] is the only approved drug in the class of HCN channel blockers.
  1. Actions
  By selectively slowing the *If* current in the SA node, ***reduction of heart rate occurs without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure***. In patients with HFrEF, a slower heart rate increases stroke volume and improves symptoms of HF.
  2. Therapeutic use
  Ivabradine is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HFpharmacotherapy. Specifically, patients should be on an optimal dose of β-blocker or have a contraindication to β-blockers.

- **3. Pharmacokinetics**
  Ivabradine should be administered with meals to increase absorption. It undergoes extensive first-pass metabolism by cytochrome P450 3A4 to an active metabolite, which is also a 3A4 substrate. *Ivabradine* has a high volume of distribution and is 70% protein bound. The half-life is 6 hours, which allows for twice-daily dosing.
  4. Adverse effects
  Bradycardia may occur with *ivabradine*, which may improve with dose reduction. Because *ivabradine* is mostly selective for the SA node, it is not effective for rate control in atrial fibrillation and has been shown to increase the risk of atrial fibrillation. *Ivabradine* inhibits similar channels in the eye, and luminous phenomena may occur early in therapy. This enhanced brightness may be ameliorated by dose reduction. *Ivabradine* should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

- **VIII. Vaso- and Venodilators**
  Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance. Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF. Arterial dilators, such as ***hydralazine*** [hye-DRAL-a-zeen], reduce systemic arteriolar resistance and decrease afterload. If the patient is intolerant of ACE inhibitors or ARBs, or if additional vasodilator response is required, a combination of ***hydralazine*** **and** ***isosorbide dinitrate*** [eye-soe-SOR-bide dye-NYE-trate] may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β- blocker plus ACE inhibitor or ARB). Headache, dizziness, and hypotension are common adverse effects with this combination. Rarely, *hydralazine* has been associated with drug-induced lupus.

- **IX. Inotropic Drugs**
  Positive inotropic agents ***enhance cardiac contractility and, thus, increase cardiac output***. Although these drugs act by different mechanisms, the **inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle**. All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF. For this reason, these agents, with the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.

- **A. Digitalis glycosides**
  The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF. The digitalis glycosides have a **low therapeutic index**, with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The only available agent is *digoxin* [di-JOX-in].

- **1. Mechanism of action**
  a. Regulation of cytosolic calcium concentration
  By inhibiting the Na+/K+-adenosine triphosphatase (ATPase) enzyme, *digoxin* reduces the ability of the myocyte to actively pump Na+ from the cell (Figure 18.8). This ultimately results in a small but physiologically important increase in free Ca2+, thereby leading to increased cardiac contractility.

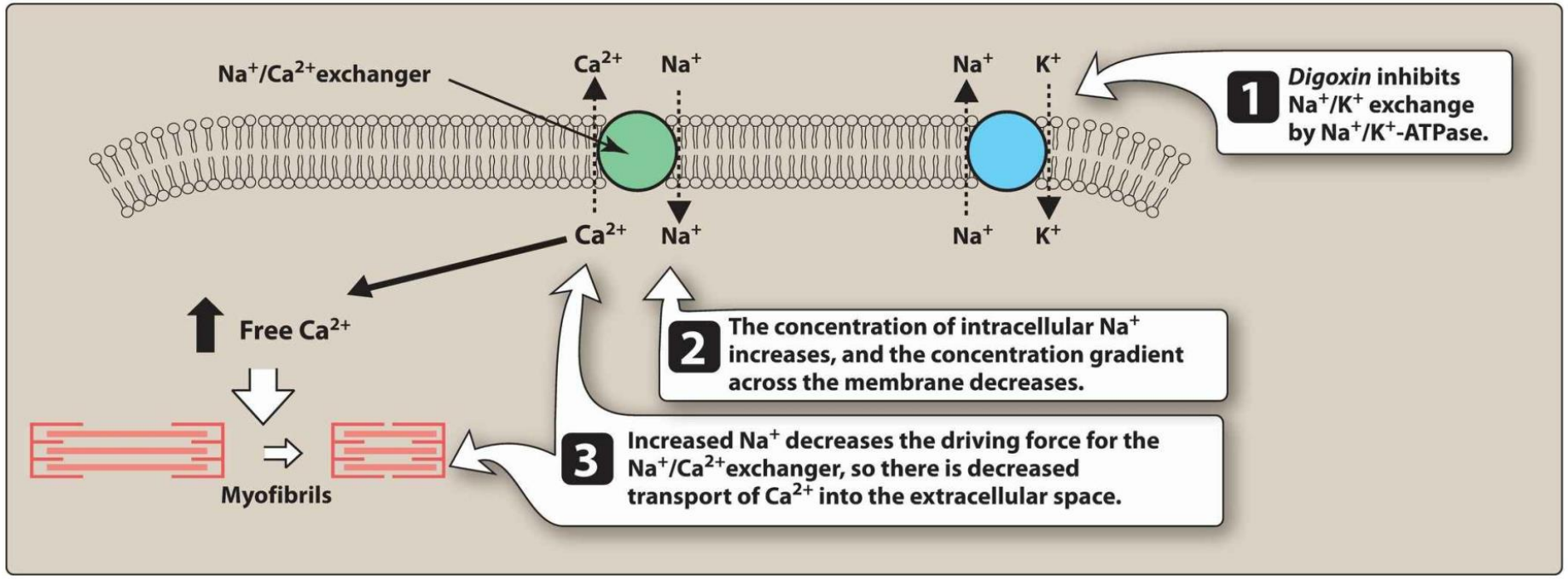
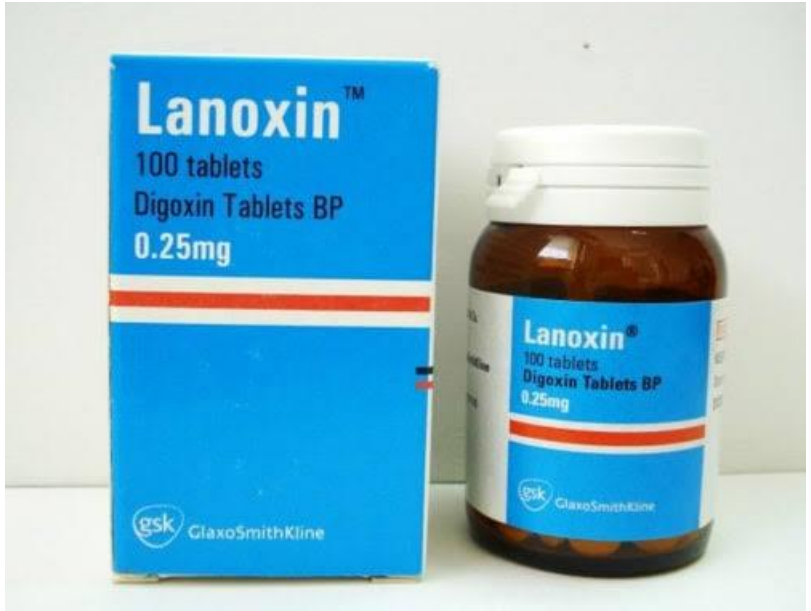
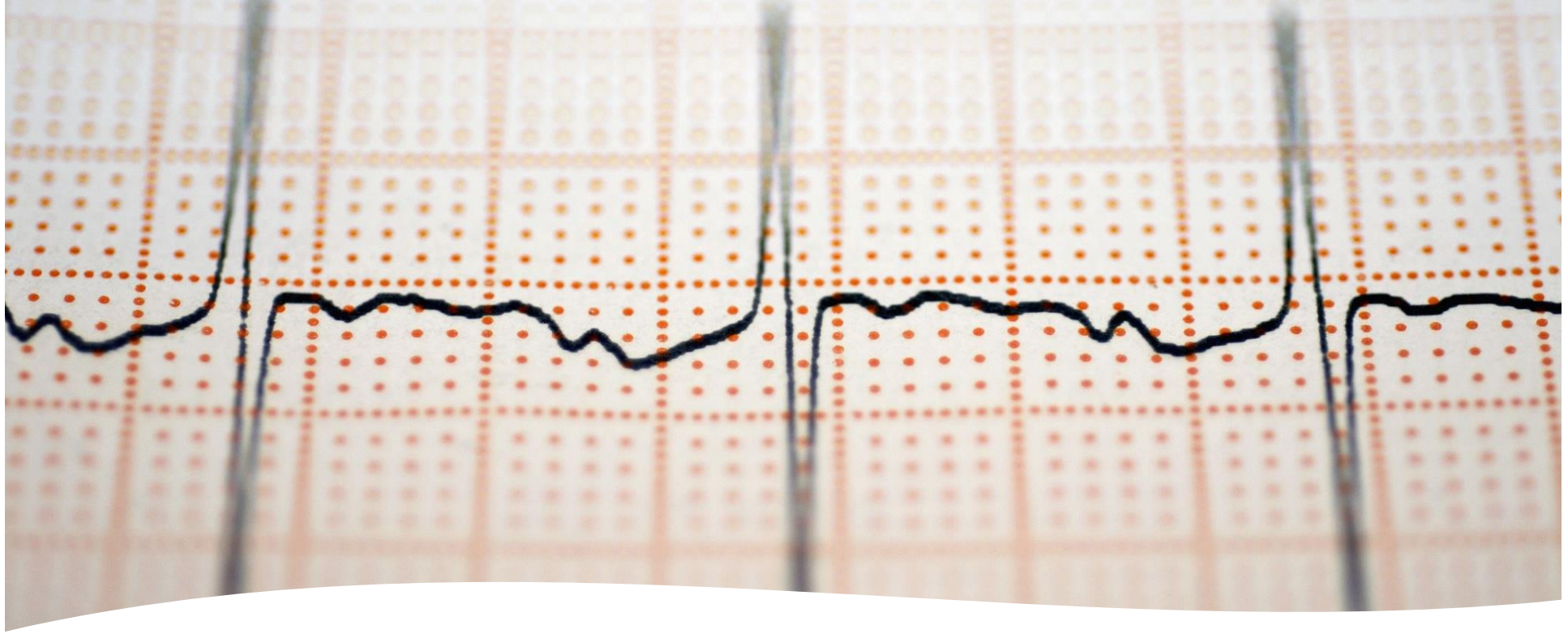


Figure 18.8 Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.





- **b. Increased contractility of the cardiac muscle**
  Digoxin increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart (Figure 18.9). *Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease.*
  Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation.

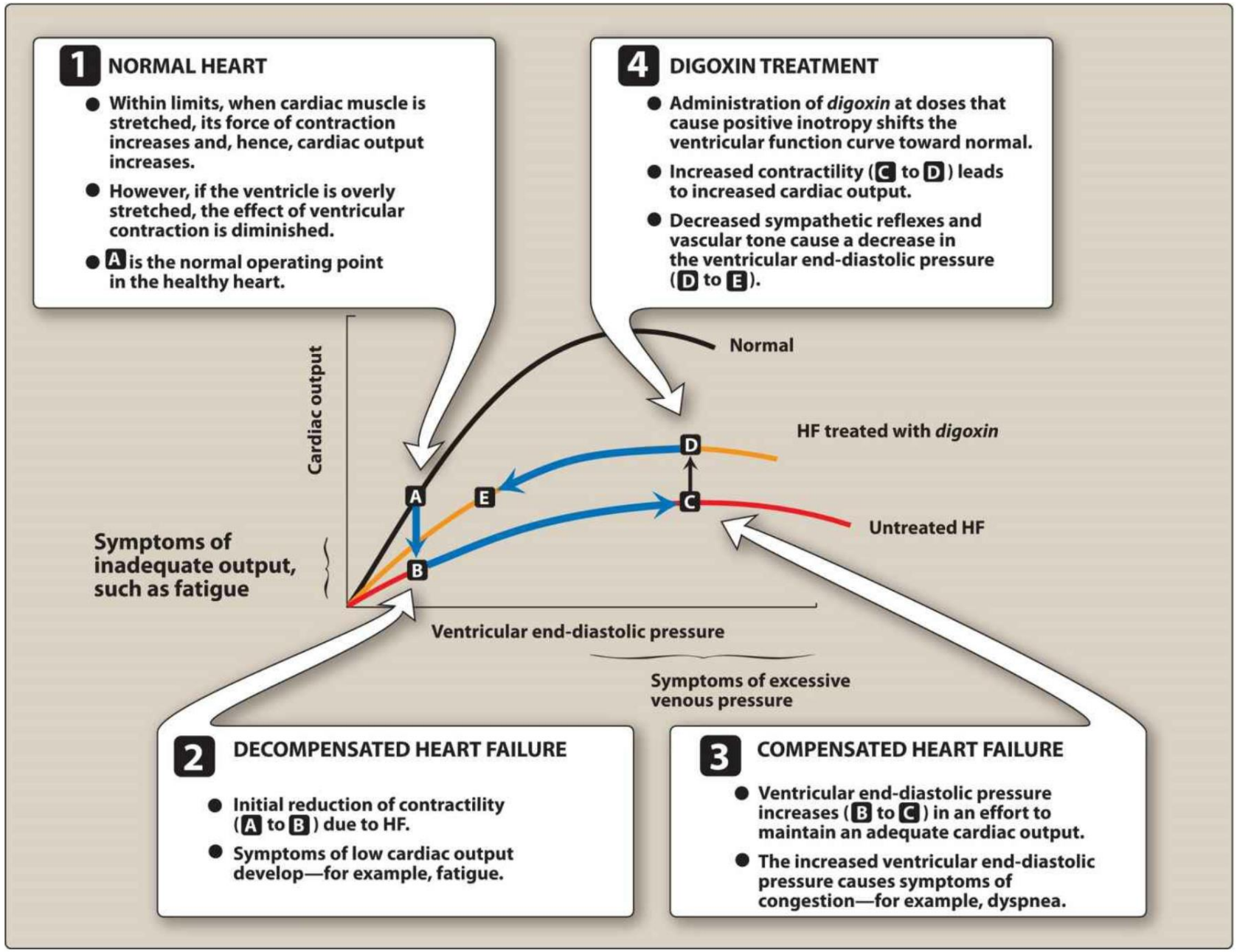


Figure 18.9 Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with *digoxin*.

- **c. Neurohormonal inhibition**
  Although the exact mechanism of this effect has not been elucidated, ***low-dose digoxin inhibits sympathetic activation with minimal effects on contractility.***

  2. Therapeutic use

  Digoxin therapy is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy. A low serum drug concentration of *digoxin* (0.5 to 0.8 ng/mL) is beneficial in HFrEF.

  3. Pharmacokinetics

  Digoxin is available in **oral** and **injectable** formulations. It has a **large volume of distribution**, because it accumulates in muscle. The dosage is based on lean body weight. In acute situations, such as symptomatic atrial fibrillation, a loading dose regimen is used. *Digoxin* **has a long half-life of 30 to 40 hours.** It is mainly **eliminated intact by the kidney**, requiring dose adjustment in renal dysfunction.

- **4. Adverse effects**
  At low serum drug concentrations, *digoxin* is well tolerated. However, it has a very narrow therapeutic index.
- ***Anorexia, nausea, vomiting, blurred vision, or yellowish vision may be initial indicators of toxicity***.
- When Na+/K+- ATPase is markedly inhibited by *digoxin*, the resting membrane potential may increase, which makes the membrane more excitable, increasing the risk of arrhythmias.
- Decreased levels of serum potassium ***(hypokalemia) predispose a patient to digoxin toxicity***, because *digoxin* normally competes with potassium for the same binding site on the Na+/K+-ATPase pump.
- With the use of a lower serum drug concentration in HFrEF, toxic levels are infrequent.
  Digoxin is a substrate of P-gp, and inhibitors of P-gp, such as clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin.
- *Digoxin* should also be used with caution with other drugs that slow AV conduction, such as β-blockers, *verapamil*, and *diltiazem*.

- **B. β-Adrenergic agonists**
  β-Adrenergic agonists, such as ***dobutamine*** [doe-BUE-ta-meen] and ***dopamine*** [DOE-pa-meen], improve cardiac performance by *causing positive inotropic effects and vasodilation*. β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction (Figure 18.10). Both drugs must be given by intravenous infusion and are primarily ***used in the short-term treatment of acute HF in the hospital setting.***

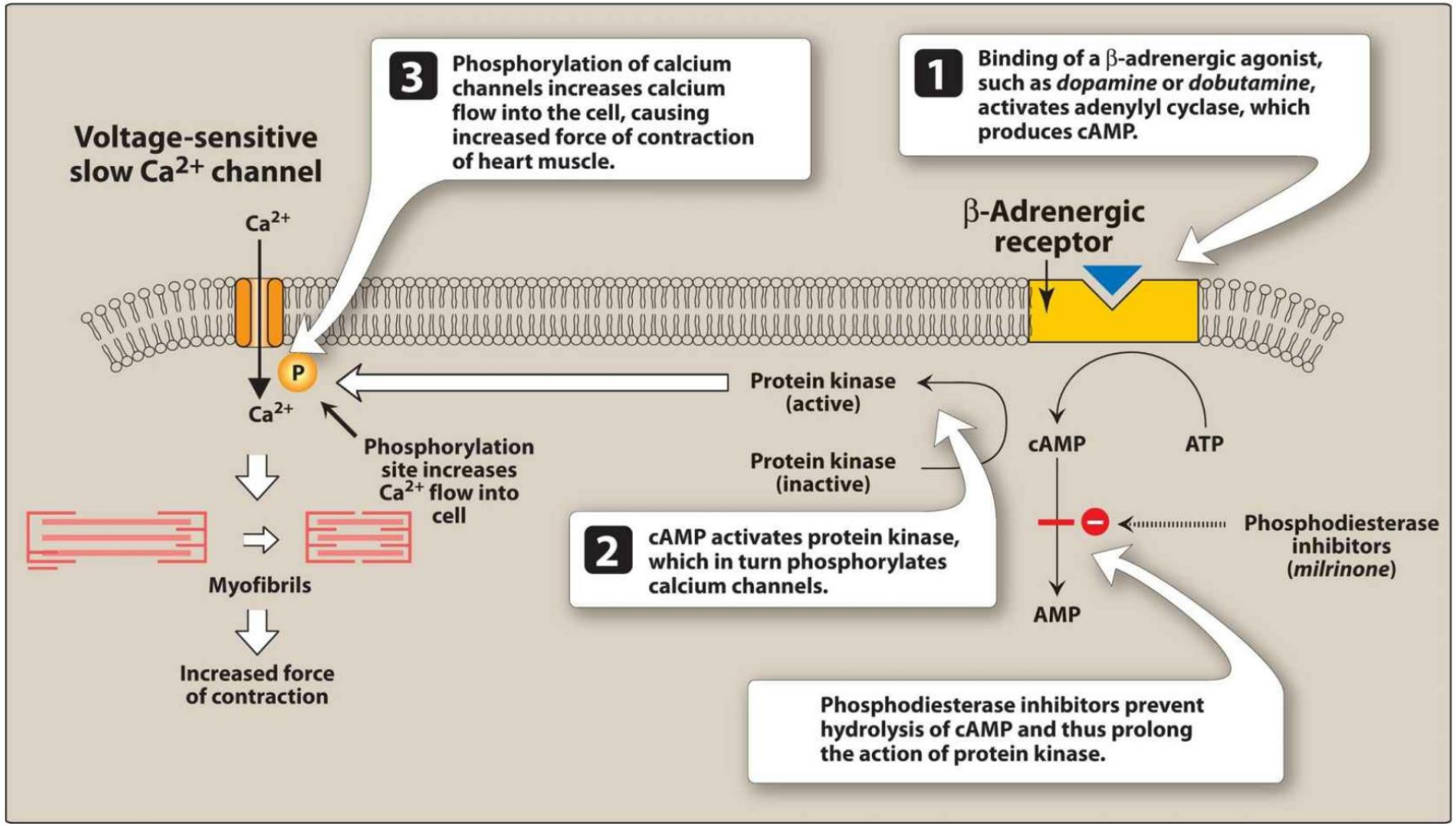
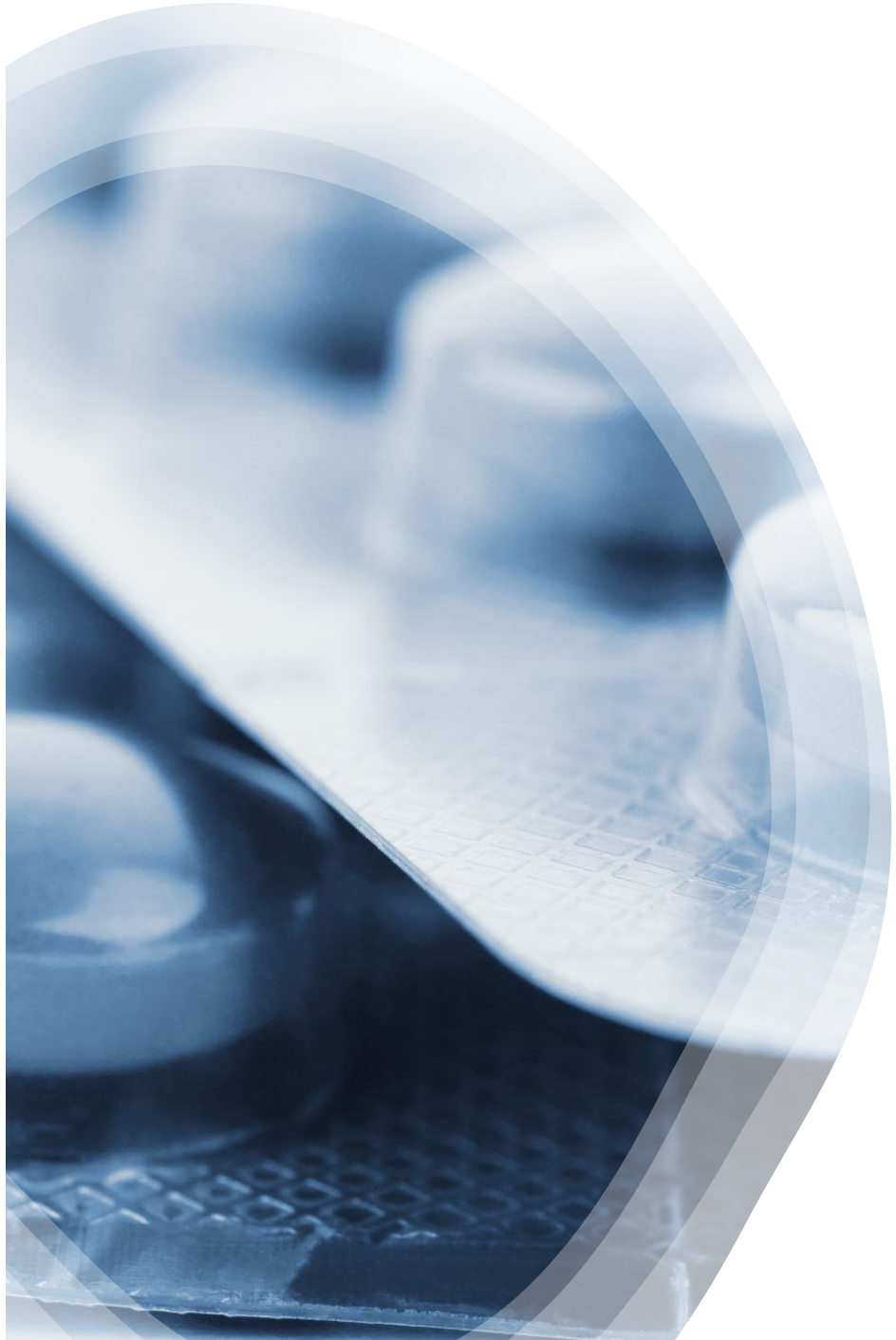


Figure 18.10 Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.



- **C. Phosphodiesterase inhibitors** ***Milrinone*** [MIL-ri-none] is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP (Figure 18.10). **Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility**. *Milrinone* is usually given by intravenous infusion for short-term treatment of acute HF. However, dobutamine and milrinone may also be considered for intermediate-term treatment in the outpatient setting for palliative care.

- **X. Recombinant B-type Natriuretic Peptide**
  In acute decompensated congestive HF, drugs that reduce preload result in improvement in HF symptoms such as dyspnea. Most often, IV diuretics are utilized in the acute setting to reduce preload. When IV diuretics are minimally effective, a recombinant B-type natriuretic peptide (BNP), or ***nesiritide*** [ness-EAR-a-tide], can be used as an alternative. Through binding to natriuretic peptide receptors, ***nesiritide*** **stimulates natriuresis and diuresis and reduces preload and afterload**. *Nesiritide* is administered intravenously as a bolus (most often) and continuous infusion.
- Like endogenous BNP, *nesiritide* has a short half-life of 20 minutes and is cleared by renal filtration, cleavage by endopeptidases and through internalization after binding to natriuretic peptide receptors. The most common adverse effects are hypotension and dizziness, and like diuretics, *nesiritide* can worsen renal function.

- **XI. Order of Therapy**
  Guidelines have classified HF into four stages, from least to most severe. Figure 18.11 shows a treatment strategy using this classification and the drugs described in this chapter. Note that as the disease progresses, polytherapy is
  initiated. In patients with **overt HF, loop diuretics** are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. **ACE inhibitors or ARBs** (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy. The dosage is gradually titrated to that which is maximally tolerated and/or produces optimal cardiac output. Historically, **β-blockers** were added after optimization of ACE inhibitor or ARB therapy; however, most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and β-blocker after initial stabilization. These agents are slowly titrated to optimal levels
  to increase tolerability. **Aldosterone antagonists** and fixed-dose ***hydralazine* and *isosorbide dinitrate*** are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.
- Once at an optimal ACE inhibitor or ARB dose and if the patient remains symptomatic, either can be replaced by *sacubitril/valsartan*. Lastly, *digoxin* and *ivabradine* are added for symptomatic benefit only in patients on optimal HF pharmacotherapy.

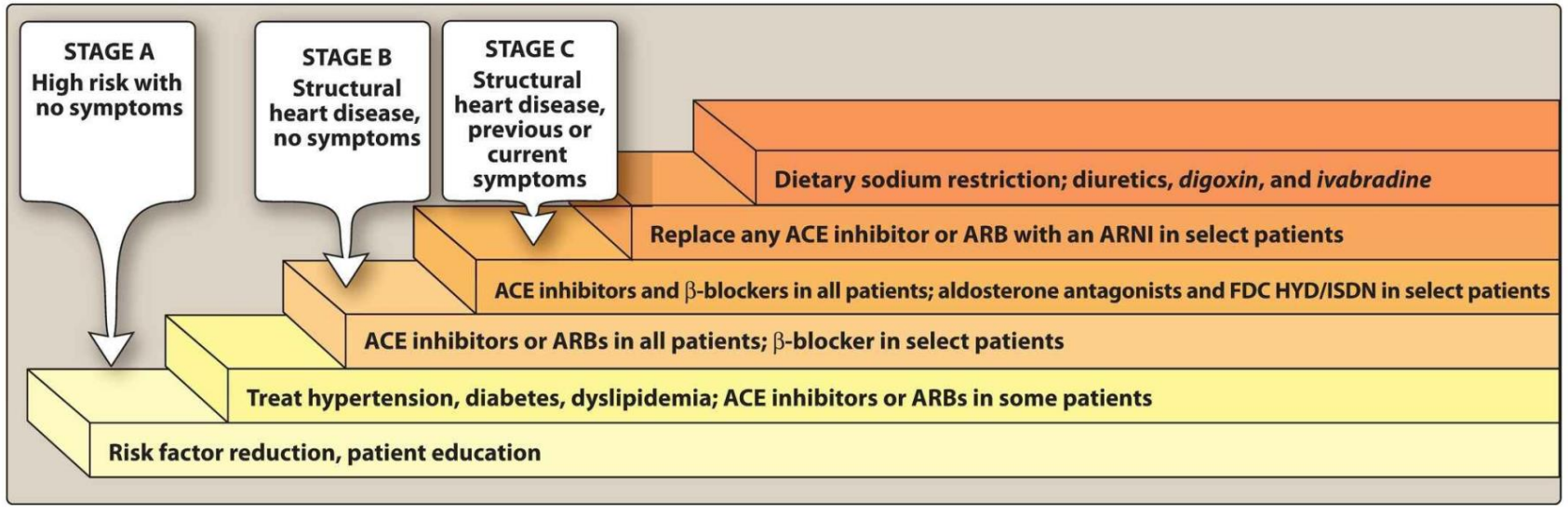


Figure 18.11 Treatment options for various stages of HF. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; FDC = fixed-dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown.

Thanks