**DPT 4th**

**Course Title: Pharmacology I**

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**Note:**

**Attempt all questions**

**Each question carry equal marks**

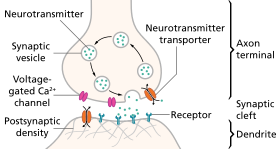
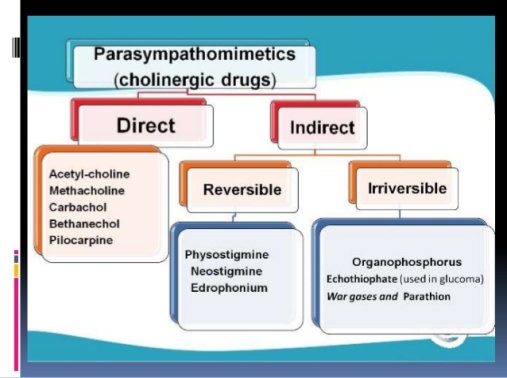
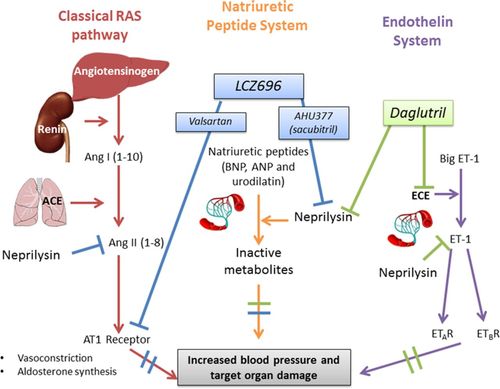
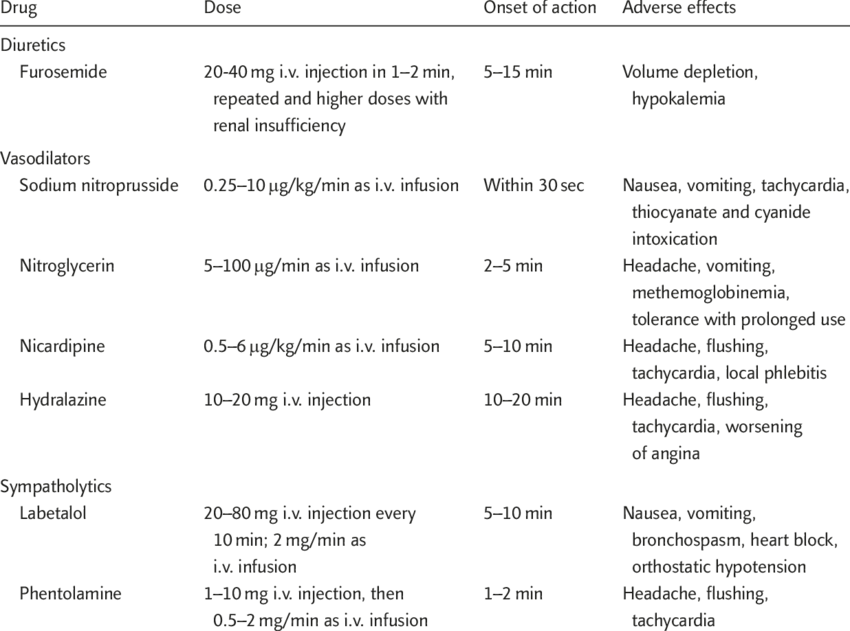
**Pay attention to every point of question**

**Give to the point answers**

**Extra detail may leads to marks deduction**

1. Explain the detailed neurotransmission process

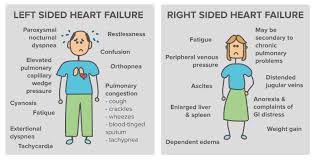
And ) Neurotransmission :

* Diagram :
* 
* Explanination:
* **Neurotransmission:**
* (Latin: *transmissio* "passage, crossing" from *transmittere* "send, let through") is the process by which signaling molecules called [neurotransmitters](https://en.wikipedia.org/wiki/Neurotransmitter) are released by the [axon terminal](https://en.wikipedia.org/wiki/Axon_terminal) of a [neuron](https://en.wikipedia.org/wiki/Neuron) (the presynaptic neuron), and bind to and react with the [receptors](https://en.wikipedia.org/wiki/Receptor_(biochemistry)) on the [dendrites](https://en.wikipedia.org/wiki/Dendrite) of another neuron (the postsynaptic neuron) a short distance away. A similar process occurs in [retrograde neurotransmission](https://en.wikipedia.org/wiki/Retrograde_neurotransmission), where the dendrites of the postsynaptic neuron release retrograde neurotransmitters (e.g., [endocannabinoids](https://en.wikipedia.org/wiki/Endocannabinoids); synthesized in response to a rise in [intracellular](https://en.wikipedia.org/wiki/Intracellular) [calcium](https://en.wikipedia.org/wiki/Calcium_in_biology) levels) that signal through receptors that are located on the axon terminal of the presynaptic neuron, mainly at [GABAergic](https://en.wikipedia.org/wiki/GABAergic) and [glutamatergic](https://en.wikipedia.org/wiki/Glutamatergic_neurotransmission) [synapses](https://en.wikipedia.org/wiki/Synapse).
* Neurotransmission is regulated by several different factors: the availability and rate-of-synthesis of the neurotransmitter, the release of that neurotransmitter, the baseline activity of the postsynaptic cell, the number of available postsynaptic receptors for the neurotransmitter to bind to, and the subsequent removal or deactivation of the neurotransmitter by enzymes or presynaptic reuptake.
* In response to a threshold [action potential](https://en.wikipedia.org/wiki/Action_potential) or [graded electrical potential](https://en.wikipedia.org/wiki/Membrane_potential#Graded_potentials), a neurotransmitter is released at the [presynaptic](https://en.wikipedia.org/wiki/Chemical_synapse) [terminal](https://en.wikipedia.org/wiki/Axon_terminal). The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an [inhibitory](https://en.wikipedia.org/wiki/Inhibitory_synapse) or [excitatory](https://en.wikipedia.org/wiki/Excitatory_synapse) way. The binding of neurotransmitters to receptors in the postsynaptic neuron can trigger either short term changes, such as changes in the [membrane potential](https://en.wikipedia.org/wiki/Membrane_potential) called [postsynaptic potentials](https://en.wikipedia.org/wiki/Postsynaptic_potential), or longer term changes by the activation of [signaling cascades](https://en.wikipedia.org/wiki/Signal_transduction).
* Neurons form complex biological neural networks through which nerve impulses (action potentials) travel. Neurons do not touch each other (except in the case of an [electrical synapse](https://en.wikipedia.org/wiki/Electrical_synapse) through a [gap junction](https://en.wikipedia.org/wiki/Gap_junction)); instead, neurons interact at close contact points called synapses. A neuron transports its information by way of an action potential. When the nerve impulse arrives at the synapse, it may cause the release of neurotransmitters, which influence another (postsynaptic) neuron. The postsynaptic neuron may receive inputs from many additional neurons, both excitatory and inhibitory. The excitatory and inhibitory influences are summed, and if the net effect is inhibitory, the neuron will be less likely to "fire" (i.e., generate an action potential), and if the net effect is excitatory, the neuron will be more likely to fire. How likely a neuron is to fire depends on how far its [membrane potential](https://en.wikipedia.org/wiki/Membrane_potential) is from the [threshold potential](https://en.wikipedia.org/wiki/Threshold_potential), the voltage at which an action potential is triggered because enough voltage-dependent [sodium channels](https://en.wikipedia.org/wiki/Sodium_channel) are activated so that the net inward sodium current exceeds all outward currents. Excitatory inputs bring a neuron closer to threshold, while inhibitory inputs bring the neuron farther from threshold. An action potential is an "all-or-none" event; neurons whose membranes have not reached threshold will not fire, while those that do must fire. Once the action potential is initiated (traditionally at the [axon hillock](https://en.wikipedia.org/wiki/Axon_hillock)), it will propagate along the axon, leading to release of neurotransmitters at the [synaptic bouton](https://en.wikipedia.org/wiki/Synaptic_bouton) to pass along information to yet another adjacent neuron.
* Stages in neuro transmission at the synapse :
* Synthesis of the neurotransmitter. This can take place in the [cell body](https://en.wikipedia.org/wiki/Cell_body), in the axon, or in the [axon terminal](https://en.wikipedia.org/wiki/Axon_terminal).
* Storage of the neurotransmitter in storage granules or vesicles in the axon terminal.
* Calcium enters the axon terminal during an action potential, causing [release](https://en.wikipedia.org/wiki/Exocytosis) of the neurotransmitter into the synaptic cleft.
* After its release, the transmitter binds to and activates a receptor in the postsynaptic membrane.
* Deactivation of the neurotransmitter. The neurotransmitter is either destroyed enzymatically, or taken back into the terminal from which it came, where it can be reused, or degraded and removed.
* Gernal discription:
* Neurotransmitters are spontaneously packed in vesicles and released in individual quanta-packets independently of presynaptic action potentials. This slow release is detectable and produces micro-inhibitory or micro-excitatory effects on the postsynaptic neuron. An action potential briefly amplifies this process. Neurotransmitter containing vesicles cluster around active sites, and after they have been released may be recycled by one of three proposed mechanism. The first proposed mechanism involves partial opening and then re-closing of the vesicle. The second two involve the full fusion of the vesicle with the membrane, followed by recycling, or recycling into the endosome. Vesicular fusion is driven largely by the concentration of calcium in micro domains located near calcium channels, allowing for only microseconds of neurotransmitter release, while returning to normal calcium concentration takes a couple of hundred of microseconds. The vesicle exocytosis is thought to be driven by a protein complex called [SNARE](https://en.wikipedia.org/wiki/SNARE_(protein)), that is the target for [botulinum toxins](https://en.wikipedia.org/wiki/Botulinum_toxins). Once released, a neurotransmitter enters the synapse and encounters receptors. Neurotransmitters receptors can either be ionotropic or g protein coupled. Ionotropic receptors allow for ions to pass through when agonized by a ligand. The main model involves a receptor composed of multiple subunits that allow for coordination of ion preference. G protein coupled receptors, also called metabotropic receptors, when bound to by a ligand undergo conformational changes yielding in intracellular response. Termination of neurotransmitter activity is usually done by a transporter , however enzymatic deactivation is also plausible.
* Summation:
* Each neuron connects with numerous other neurons, receiving numerous impulses from them. **Summation** is the adding together of these impulses at the axon hillock. If the neuron only gets excitatory impulses, it will generate an action potential. If instead the neuron gets as many inhibitory as excitatory impulses, the inhibition cancels out the excitation and the nerve impulse will stop there.Action potential generation is proportionate to the probability and pattern of neurotransmitter release, and to postsynaptic receptor sensitization.
* **Spatial summation** means that the effects of impulses received at different places on the neuron add up, so that the neuron may fire when such impulses are received simultaneously, even if each impulse on its own would not be sufficient to cause firing.
* **Temporal summation** means that the effects of impulses received at the same place can add up if the impulses are received in close temporal succession. Thus the neuron may fire when multiple impulses are received, even if each impulse on its own would not be sufficient to cause firing.
* Convergence and divergence :
* Neurotransmission implies both a convergence and a divergence of information. First one neuron is influenced by many others, resulting in a convergence of input. When the neuron fires, the signal is sent to many other neurons, resulting in a divergence of output. Many other neurons are influenced by this neuron.
* Cotransmission :
* **Cotransmission** is the release of several types of neurotransmitters from a single [nerve terminal](https://en.wikipedia.org/wiki/Nerve_terminal).
* At the nerve terminal, neurotransmitters are present within 35–50 nm membrane-encased vesicles called [synaptic vesicles](https://en.wikipedia.org/wiki/Synaptic_vesicle). To release neurotransmitters, the synaptic vesicles transiently dock and fuse at the base of specialized 10–15 nm cup-shaped [lipoprotein](https://en.wikipedia.org/wiki/Lipoprotein) structures at the presynaptic membrane called [porosomes](https://en.wikipedia.org/wiki/Porosomes). The neuronal porosome [proteome](https://en.wikipedia.org/wiki/Proteome) has been solved, providing the molecular architecture and the complete composition of the machinery.
* Recent studies in a myriad of systems have shown that most, if not all, neurons release several different chemical messengers. Cotransmission allows for more complex effects at [postsynaptic receptors](https://en.wikipedia.org/wiki/Neurotransmitter_receptor), and thus allows for more complex communication to occur between neurons.
* In modern neuroscience, neurons are often classified by their cotransmitter. For example, striatal "GABAergic neurons" utilize [opioid peptides](https://en.wikipedia.org/wiki/Opioid_peptide) or [substance P](https://en.wikipedia.org/wiki/Substance_P) as their primary cotransmitter.
* Some neurons can release at least two neurotransmitters at the same time, the other being a cotransmitter, in order to provide the stabilizing negative feedback required for meaningful encoding, in the absence of inhibitory [interneurons](https://en.wikipedia.org/wiki/Interneuron). Examples include:
* [GABA](https://en.wikipedia.org/wiki/GABA)–[glycine](https://en.wikipedia.org/wiki/Glycine) co-release.
* [Dopamine](https://en.wikipedia.org/wiki/Dopamine)–[glutamate](https://en.wikipedia.org/wiki/Glutamate) co-release.
* [Acetylcholine](https://en.wikipedia.org/wiki/Acetylcholine) (Ach)–glutamate co-release.
* ACh–[vasoactive intestinal peptide](https://en.wikipedia.org/wiki/Vasoactive_intestinal_peptide) (VIP) co-release.
* ACh–[calcitonin gene-related peptide](https://en.wikipedia.org/wiki/Calcitonin_gene-related_peptide) (CGRP) co-release.
* Glutamate–[dynorphin](https://en.wikipedia.org/wiki/Dynorphin) co-release (in [hippocampus](https://en.wikipedia.org/wiki/Hippocampus)).
* [Noradrenaline](https://en.wikipedia.org/wiki/Norepinephrine) and [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate) are [sympathetic](https://en.wikipedia.org/wiki/Sympathetic_nervous_system) co-transmitters. It is found that the endocannabinoid [anadamide](https://en.wikipedia.org/wiki/Anandamide) and the [cannabinoid](https://en.wikipedia.org/wiki/Cannabinoid), [WIN 55,212-,2](https://en.wikipedia.org/wiki/WIN_55,212-2) can modify the overall response to sympathetic nerve stimulation, and indicate that prejunctional [CB1 receptors](https://en.wikipedia.org/wiki/Cannabinoid_receptor_type_1) mediate the [sympatho](https://en.wikipedia.org/wiki/Sympathomimetic_drug)-inhibitory action. Thus cannabinoids can inhibit both the noradrenergic and [purinergic](https://en.wikipedia.org/wiki/Purinergic_signalling) components of sympathetic neurotransmission.
* One unusual pair of co-transmitters is GABA and glutamate which are released from the same axon terminals of neurons originating from the [ventral tegmental area](https://en.wikipedia.org/wiki/Ventral_tegmental_area) (VTA), [internal globus pallidus](https://en.wikipedia.org/wiki/Internal_globus_pallidus), and [supramammillary nucleus](https://en.wikipedia.org/wiki/Supramammillary_nucleus). The former two project to the [habenula](https://en.wikipedia.org/wiki/Habenula) whereas the projections from the supramammillary nucleus are known to target the [dentate gyrus](https://en.wikipedia.org/wiki/Dentate_gyrus) of the hippocampus.
* Genetic association :
* Neurotransmission is genetically associated with other characteristics or features. For example, [enrichment analyses](https://en.wikipedia.org/wiki/Gene_set_enrichment) of different signaling pathways led to the discovery of a genetic association with intracranial volume.
* Short summry :
  + [Neurotransmission](https://www.sciencedirect.com/topics/neuroscience/neurotransmission) is the fundamental process that drives information transfer between neurons and their targets. It regulates both excitatory and inhibitory functions in the central nervous system (CNS), underlies [sensory processing](https://www.sciencedirect.com/topics/neuroscience/sensory-processing), and regulates autonomic and motor outputs in species ranging from small invertebrates to highly evolved mammals. Modulation of [synaptic transmission](https://www.sciencedirect.com/topics/neuroscience/synaptic-transmission) is believed to drive cognitive processes such as learning and memory. Neurotransmission occurs at specialized regions between neurons and their targets, called the [synapse](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/synapse). The synapse is a highly specialized contact between a presynaptic and a postsynaptic cell built to transmit information with high fidelity. [Synaptic transmission](https://www.sciencedirect.com/topics/neuroscience/synaptic-transmission) is mediated by repeated cycles of [exocytosis](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/exocytosis) of [neurotransmitters](https://www.sciencedirect.com/topics/neuroscience/neurotransmitters) followed by [endocytosis](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/endocytosis) of [synaptic vesicles](https://www.sciencedirect.com/topics/neuroscience/synaptic-vesicle) (SVs) at nerve terminals. . Neuronal exocytosis is the final step in a cycle that leads to information transfer across [synapses](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/synapse). The vesicle cycle is highly regulated via essential vesicular and plasma [membrane proteins](https://www.sciencedirect.com/topics/neuroscience/transmembrane-protein) that mediate the various steps including [neurotransmitter](https://www.sciencedirect.com/topics/neuroscience/neurotransmitters) loading into vesicles, docking, priming, calcium sensing, exocytosis, and recycling. Despite the progress in understanding the roles of individual proteins using physiological, biochemical, and genetic methods, much remains unknown regarding the sequence and kinetics of [protein–protein interactions](https://www.sciencedirect.com/topics/neuroscience/protein-protein-interaction) that drive vesicle recycling.
* What does direct and indirect cholinergic agent means? Explain therapeutic application and adverse effects of cholinergic agents in detail.
* Ans ) Cholinergic agents :
* Defination :
* Cholinergic Agonists are drugs that lead to stimulation of cholinergic receptors which include [nicotinic](http://www.pathwaymedicine.org/Nicotinic-Receptor) and [muscarinic receptors](http://www.pathwaymedicine.org/muscarinic-receptor). Given the broad function of cholinergic receptors in the CNS, [autonomic nervous system](http://www.pathwaymedicine.org/autonomic-nervous-system), and neuromuscular junction, cholinergic agonists have broad pharmacological effects which limit their therapeutic usefulness. These drugs can be divided into direct-acting agonists that directly bind cholinergic receptors or indirect-acting agonists that inhibit destruction of acetylcholine at cholinergic synapses (i.e. anticholinesterases).
* Mechanisms of action :
* **Direct Cholinergic Agonists**
  + These drugs directly bind and activate nicotinic and muscarinic receptors with variable amounts of selectivity.
* **Indirect Cholinergic Agonists: The Anticholinesterases** :
  + These drugs inhibit [anticholinesterase](http://www.pathwaymedicine.org/anticholinesterase) the enzyme which destroys [acetylcholine](http://www.pathwaymedicine.org/acetylcholine) secreted into the synapse by the [cholinergic neuron](http://www.pathwaymedicine.org/cholinergic-neuron). By inhibiting destruction these drugs extend the the half-life of synaptic acetylcholine and thus boost systemic cholinergic activity.
* Drugs classes :
* **Direct Cholinergic Agonists**
  + [Acetylcholine](http://www.pathwaymedicine.org/Acetylcholine)
  + [Bethanechol](http://www.pathwaymedicine.org/Bethanechol)
  + [Carbachol](http://www.pathwaymedicine.org/Carbachol)
  + [Pilocarpine](http://www.pathwaymedicine.org/Pilocarpine)
* [**Anticholinesterases**](http://www.pathwaymedicine.org/Anticholinesterase)
* Difference between direct and indirect
* 
* Explain therapeutic application and adverse effects of cholinergic agents in detail.
* Ans )
* **Myasthenia Gravis**
* Myasthenia gravis is an autoimmune disorder that attacks the nicotinic ACh receptors at the neuromuscular junction
  + leads to profound **muscle weakness**
* Acetylcholinesterase inhibitors **increase the amount of acetylcholine** in the neuromuscular junction
  + neostigmine is frequently used for this disorder
* If muscarinic side-effects are prominent, anticholinergics can be administered (e.g., atropine)
  + tolerance usually occurs to the muscarinic side-effects
  + 2. Reversal of NeuroMuscularBlockade:
* By increasing levels of acetylcholine in the NMJ, the compounds are able to facilitate recovery from competitive neuromuscular blockade
  + restores neuromuscular transmission
* 3. Glaucoma
* Constriction of the ciliary body **promotes aqueous humor outflow** --> decreased intraoccular pressure
* Direct and indirect cholinomimetics can be used to treat glaucoma
* **pilocarpine** is the most commonly used agent
* typically formulated as eye drops
  + 4. Atonic GI/GU
* The smooth muscle of the GI and GU systems can show depressed activity in certain states
  + post-operative ileus
  + congenital megacolon
* Bethanechol and neostigmine are the most widely used agents
  + increases secretion and motility in the G.I. tract
  + can be given orally or by injection.
* These agents can not be used if there is a mechanical obstruction of the GI or urinary tract.
  + **e. Adverse effects of cholinergic agents**
  + The primary adverse effects of cholinergic stimulants include gastrointestinal distress (**nausea, vomiting, diarrhea, abdominal cramping**), increased salivation, bronchoconstriction, bradycardia, and difficulty in visual accommodation.
* Short summery :
* **Cholinomimetic drugs;**
* **Classification :**
* Drugs that Increase Cholinergic Activity
* Cholinergic agonists (direct acting)
* muscarinic agonists (pilocarpine)
* nicotinic agonists (nicotine)
* Inhibitors of acetylcholinesterase (indirect acting)
* reversible inhibitors (neostigmine)
* irreversible inhibitors (nerve gas, insecticides
* MECHANISM OF ACTION :
* Muscarinic receptors are coupled to G-proteins that activate phospholipase C (M1 and M3) or inhibit adenylyl cylase (M2)
* increased production of IP3 and DAG, decreased levels of cAMP
* These second messengers produce a number of intracellular effects
* increase intracellular Ca2+ levels and activation of protein kinase C
* opening of K+ channels --> hyperpolarization of the cell
* Activation of nicotinic receptors produces an influx of Na+ ions and depolarization of the cell --> action potential
* . Organ System Effects
* . Cardiovascular system:
* Primary effects of muscarinic agonists are a **decrease in peripheral resistance** and **changes in heart rate**
* Direct effects of the heart include:
  + **increased K+ current** in atrial muscle, SA and AV nodes
  + **decreased Ca2+ current** in cardiac cells
  + a **reduction in hyperpolarization-activated** current that underlies diastolic depolarization
* net effect is to slow the pace maker cells and decrease atrial contractility
  + the ventricles are less densely innervated than the atrial tissue
* The direct effects of muscarinic agonists on the heart are usually opposed by reflex sympathetic discharge
  + elicited by the fall in blood pressure
* Muscarinic agonists **can produce marked vasodilation**
  + generation of EDRF from endothelial cells (Nitric Oxide main contributor)
* . Respiratory system: (bronchoconstriction)
* Muscarinic agonists produce smooth muscle contraction and stimulate secretion in the bronchial tree
* can aggravate symptoms associated with asthma .
* . Genitourinary tract: (urination)
* Stimulation of muscarinic receptors **increases tone of the detrusor** muscle and **relaxes the trigone and sphincter** muscles of the bladder
* promotes voiding of urine
* No major effects on uterine contractility
* . Eye: (miosis)
* muscarinic stimulation leads to contraction of the smooth muscle of the iris sphincter and of the cilliary muscle
* responsible for miosis and accomodation, respectively
* Both effects promote the outflow of aqueous humor
* decreases intraoccular pressure
* 5. Miscellaneous secretory glands: (secretions)
* muscarinic agonists stimulate the secretory activity of sweat, lacrimal and nasopharyngeal glands
* 6. CNS effects:
* The CNS contains both **muscarinic and nicotinic** receptors
* ***Nicotine*** has important effects on the **brainstem and cortex**
* **stimulant** type effects, addiction liability
* high doses can cause **tremor and convulsions**
* ***Muscarinic*** receptors play a role in **movement, cognition, learning and memory, and vestibular function**
* potential therapeutic applications to CNS diseases, though side-effects limit the clinical use of these agents
* Neuromuscular junction:
* nicotine receptors **initiate muscle action potentials**
* **fasciculations** to strong contractions of an entire muscle possible
* can produce **depolarization blockade**
* Indirect Acting Cholinomimetics :
* . Mechanism of action
* Indirect-acting parasympathomimetics inhibit the enzymatic destruction of acetylcholine by inactivating cholinesterase, leaving acetylcholine free to act on the effector cells.
* **Organ System Effects :**
* 1.Cardiovascular system:
* Net effect of moderate doses is modest bradycardia and a fall in CO, with only minimal effects on blood pressure
* higher doses produce marked bradycardia and hypotension
* 2. Respiratory, GI and GU systems:
* Similar to effects produced by direct acting agents
* 3. Neuromuscular junction:
* Low (therapeutic) doses prolong and intensify the effects of physiologically released acetylcholine
* Higher doses can lead to muscle fibrillation and fasiculations of an entire motor unit.
* Explain the effects and adverse effects of organic nitrates in angina pectoris.
* Write down the treatment algorithm for improving symptoms of stable angina.
* Ans ) (a) Explain the effects and adverse effects of organic nitrates in angina pectoris
* Effect of organic nitrates in angina pectoris
* Nitrates are very effective antianginal and anti-ischaemic agents. Provision of a long nitrate-free interval or low plasma nitrate levels prior to the morning dose prevents the loss of clinical efficacy by preventing the development of tolerance. However, side effects during nitrate therapy are common. Headache is the most common side effect of nitrates; often dose-related and reported by up to 82% of patients in placebo-controlled trials. Nearly 10% of patients are unable to tolerate nitrates due to disabling headaches or dizziness. In others, headaches are mild-to-moderate in severity and either resolve or diminish in intensity with continued nitrate therapy. Nitrate-induced hypotension is common, but often asymptomatic. In rare instances, nitrate-induced hypotension is severe and accompanied by marked slowing of the heart rate and syncope. Use of nitrates in patients who experience syncope after administration of nitrates is contraindicated. Nitrates rarely cause coronary steal and myocardial ischaemia. Nitrate rebound may occur and patients may experience nocturnal anginal episodes during intermittent therapy with nitroglycerin patches. Administration of nitrates is contraindicated with concomitant use of phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction, as combination therapy may lead to profound hypotension and even death. There are disturbing observational reports in the literature that continuous, prolonged use of nitrates may lead to increased mortality and recurrent myocardial infarctions. Large, randomised, placebo-controlled studies are needed to confirm or refute these reports; until then, the use of nitrates to treat angina is here to stay.
* Adverse effect of angina pectoris
* Although the exposure of human subjects to prostacyclin (PGI2) infusion has been broad, no systematic approaches have been made in order to investigate the dose-related side effects in patients with angina pectoris and coronary artery disease (CAD). We studied 25 patients with typical chest pain and overt CAD. All patients underwent a cycloergometer stress testing (25 W increments at 2-min intervals). PGI2 was infused in scalar doses up to 10 ng/kg/min. During the infusion 25 patients (100%) had facial flushing, 7 (28%) moderate headache and one (4%) had nausea. In addition, 4 patients experienced the typical chest pain and had significant (greater than or equal to 0.1 mV) ST segment depression at 8.10 ng/kg/min infusion rates. These patients had lower tolerance to exercise (6.7 +/- 1.7 vs. 8.8 +/- 1.9 min; p less than 0.05) and coronary artery lesions more severe than those observed in patients without drug-induced angina pectoris. Our data therefore indicate that PGI2 at therapeutic doses may induce myocardial ischemia in patients with angina pectoris, low tolerance to exercise and severe CAD. In patients with mild to moderate degree of CAD, PGI2 was found to be well tolerated. These findings suggest that patients with angina pectoris and low tolerance to exercise should be excluded from clinical studies directed at elucidating the effectiveness of PGI2 in cardiovascular disorders.
* (b)Write down the treatment algorithm for improving symptoms of stable angina?
* Ans )
* Chronic stable angina is the most common manifestation of ischaemic heart disease in the developed world and is associated with impaired quality of life and increased mortality. The pathogenesis of stable angina is complex and often, albeit not always, involves flow-limiting epicardial coronary artery stenoses (atheromatous plaques) that reduce the ability of the coronary circulation to deliver appropriate blood supply to the myocardium. The coronary microcirculation can also play an important role. An imbalance between myocardial oxygen supply and metabolic oxygen demand causes the symptoms of angina pectoris and represents a major therapeutic target. Rational treatment requires a multi-faceted approach combining lifestyle changes, aggressive management of modifiable coronary artery disease risk factors, pharmacological therapy and myocardial revascularisation when appropriate. Despite modern therapies, many patients continue to suffer from angina. Several new anti-anginal drugs have been introduced that might allow more effective symptom control. These novel agents have specific mechanisms of action and fewer side effects compared to conventional drugs. The combined use of traditional and novel treatments is likely to increase the proportion of patients who are managed successfully with medical therapy alone. This article briefly reviews recent advances in the pharmacological management of chronic stable angina pectoris, highlighting how an understanding of the prevailing pathogenic mechanisms in the individual patient can aid appropriate selection of therapeutic strategies and improve clinical outcome.
* Introduction
* Current treatment strategies for chronic stable angina aim to control symptoms, reduce the ischaemic burden and improve prognosis by preventing the progression of atherosclerotic coronary artery disease (CAD) and its consequences. Ideally, the treatment of angina should be tailored to the individual patient's needs, taking into consideration the characteristics and severity of symptoms, the location, severity and functional significance of coronary artery stenoses, the presence of co-morbidities and patient preference. For each individual patient, the efficacy of the agent and their side effects, together with patient compliance, are important determinants for the success or the failure of a given treatment .
* Overview of chronic stable angina
* The term angina pectoris refers to William Heberden's classic description of the clinical symptoms of angina, as reported to the Royal College of Physicians in 1768  There is currently no systematically agreed definition for angina pectoris and the term is used to define both the typical chest pain associated with myocardial ischaemia and the syndrome characterised by chest pain, myocardial ischaemia and obstructive atherosclerotic coronary artery disease. In this article, we use the term ‘angina’ in relation to the occurrence of typical central chest pain associated with myocardial ischaemia, irrespective of the presence or absence of flow-limiting organic coronary artery stenosis.
* Angina is considered to be ‘chronic’ and ‘stable’ when symptoms are present for at least two months, without changes in severity, character or triggering circumstances
* Stable angina is the most common clinical manifestation of ischaemic heart disease, affecting 58% of patients with CAD. Its prevalence increases with age, rising from roughly 8% in men and 3% in women aged 55–64 years, to 14% in men and 8% in women aged 65–74 years, in England The annual mortality rate resulting from coronary heart disease in patients with stable angina is 0.9–1.4% per year
* Stable angina results from an imbalance between coronary blood supply and myocardial oxygen demand, which is often, but not always, associated with the presence of obstructive CAD. Transient myocardial ischaemia typically causes ‘constrictive’ chest discomfort, resulting from the activation of mechano- and chemo-sensitive myocardial receptors. Patients with stable angina might or might not present with typical symptoms, and ‘silent’ myocardial ischaemia can be present in patients with diabetes mellitus and in the elderly. The typical clinical characteristics of chronic stable angina are summarised in
* [[An external file that holds a picture, illustration, etc.
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* Pathophysiological and pathogenic mechanisms: determinants of clinical presentation
* The pathogenesis of angina is often multi-factorial. The basic underlying mechanism that leads to angina is an imbalance of myocardial oxygen supply and demand. This often occurs as a direct result of flow-limiting CAD, but it can also be due to coronary artery spasm limiting blood supply, coronary microvascular dysfunction and/or several other contributing mechanisms. To a great extent, the underlying pathogenic mechanism determines the pattern of clinical presentation, leading to effort-induced angina, mixed angina or angina at rest.
* Effort-induced angina
* Long-standing obstructive epicardial CAD causes angina by providing a fixed limitation of coronary blood flow, which prevents physiological matching of coronary blood supply to exercise-induced increases in myocardial metabolic demand. A stenosis of 50% or more in the left main coronary artery, or 70% or more in another major epicardial artery, is defined as ‘obstructive’.[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R6) Symptoms of effort-induced stable angina resulting from flow-limiting coronary stenoses often occur at a predictable and reproducible threshold, triggered by physical activity and/or emotional stress. The Canadian Cardiovascular Society (CCS) grading of angina is a functional classification of exercise tolerance that can be related to metabolic equivalent units (METs) and it is used in the assessment of exercise stress testing.
* ‘Mixed’ angina
* The imbalance of myocardial oxygen supply and demand in angina can also result from combined mechanisms. Excessive coronary artery vasoconstriction at the site of organic stenoses manifests clinically as ‘mixed angina pectoris’, in which patients present with variable-threshold effort angina and occasionally angina at rest.
* Microvascular angina
* Coronary microvascular resistance is the main determinant of coronary flow reserve (the ratio of maximal induced myocardial flow to resting coronary blood flow). Abnormal vasodilatory responses of the coronary microcirculation can cause effort-related angina (microvascular angina). It is important to note that as few as 38% of patients without previously known heart disease who undergo elective diagnostic coronary angiography are found to have obstructive CAD. In many of these patients with typical angina symptoms, exercise-induced myocardial ischaemia is caused by coronary microvascular dysfunction. Patients with cardiac syndrome X — defined as typical exertional angina, positive stress test responses and normal coronary angiograms — experience transient myocardial ischaemia resulting from impaired endothelial function, which leads to abnormal coronary microvascular vasodilatation, increased coronary vasoconstriction, or both.
* In the ACOVA (Abnormal Coronary VAsomotion in patients with stable angina and unobstructed coronary arteries) study, approximately two-thirds of patients without significant epicardial CAD had positive intra-coronary acetylcholine tests for distal epicardial or microvascular spasm. Clinicians should be encouraged to think about the possibility of microvascular dysfunction or coronary microvascular spasm in patients who present with typical angina despite having angiographically normal coronary arteries.
* Other contributing mechanisms
* Following transient myocardial ischaemia, impaired diastolic relaxation and increased wall tension caused by calcium overload, which results from intracellular acidosis, and activation of late inward sodium currents worsens the oxygen imbalance and prolongs the angina episode.Further metabolic derangement, including abnormalities of substrate supply and utilisation, enzymatic activities and mitochondrial function, can also contribute to the pathogenesis. Aortic stenosis, hypertrophic cardiomyopathy, severe anaemia and thyrotoxicosis (when present) are other potential contributory factors that can worsen myocardial ischaemia.
* Diagnosis and management
* Importance of the clinical history for diagnosis and management of stable angina pectoris
* The accurate diagnosis of chronic stable angina (and the recognition of possible underlying pathogenic mechanisms) relies largely on obtaining a detailed clinical history. The severity of chest pain does not necessarily correlate to the extent of underlying CAD, but the burden of symptoms experienced by an individual patient will guide the nature and extent of the anti-anginal treatments used.
* The CCS classification of angina can provide clinically useful diagnostic and prognostic clues that are important for patient management. In CCS grade I patients, angina is only precipitated by strenuous or severe and prolonged exertion; whereas at the other end of the spectrum, CCS grade IV patients, develop angina with minor exertion or even at rest. It is important to remember that CCS grade does not necessarily reflect CAD severity  By contrast, the occurrence of chest pain with progressively increased frequency and/or severity (‘crescendo’ angina), compared to the usual chronic stable symptoms, can be an expression of acute coronary syndrome (unstable angina and myocardial infarction) and must be monitored carefully and investigated promptly.
* Diagnostic investigation
* Further investigation is guided by a risk stratification that is based on pre-test probability, derived from age, sex, character of symptoms and cardiovascular risk factors, as outlined by the NICE (National Institute for Health and Clinical Excellence) guideline on chest pain.[15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R15) For low-risk CAD patients (10–29%) with stable symptoms, NICE recommends CT coronary calcium scoring as the first-line investigation.[15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R15) While the reasons behind this recommendation are sound, the practical implementation of this strategy is not always feasible or straightforward, and cardiologists often resort to alternative diagnostic testing with stress echocardiography or even exercise stress testing. Functional imaging with stress echocardiography, nuclear myocardial perfusion scanning or first-pass cardiac magnetic resonance scanning is advised for patients with moderate cardiovascular risk (30–60%). For high-risk patients (61–90%), NICE recommends proceeding directly to invasive coronary angiography  The use of ECG exercise tolerance testing to diagnose CAD is not recommended, albeit this relatively inexpensive test can often give useful functional information and, in practice, is still a useful diagnostic tool.
* Pharmacological management of angina pectoris
* Although the general principles of treatment (ie lifestyle modification and risk-factor management) are applicable to all patients with angina, treatment should be individualised where possible. It should aim to reverse or reduce the underlying pathophysiological mechanisms in order to relieve symptoms and improve cardiovascular risk profile. Key interventions include lifestyle changes (eg smoking cessation, dietary modification and increased physical exercise), management of hypertension, diabetes and obesity, and other secondary cardiovascular disease prevention measures, such as the use of anti-platelet and lipid-lowering agents, pharmacological anti-anginal therapies and percutaneous and/or surgical revascularisation when appropriate.
* [Fig 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/figure/figure1/) provides a proposed practical therapeutic algorithm that is based on recently updated NICE guidelines, and [Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/table/table1/) summarises important clinical information for each of the currently used anti-anginal agents included in this treatment algorithm.
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* [Fig 1.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/figure/figure1/)
* **Proposed practical algorithm for pharmacological treatment of chronic stable angina based on NICE guidance.**[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R4) BB = beta-blocker; CCB = calcium channel blocker; DM = diabetes mellitus; GTN = glyceryltrinitrate; HF = heart failure; MI = myocardial infarction. \*added cardio-protective properties; †improves HbA1c in DM; ‡prognostic benefit in HF.
* Table 1.
* Summary of anti-anginal drugs supported by NICE guidance.[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R4)
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* Treatment of chest pain episodes
* Episodes of angina are best treated with sublingual glyceryltrinitrate (GTN). GTN acts as a nitric oxide donor, causing systemic and coronary vasodilatation. GTN is rapidly absorbed in the sublingual mucosae and its effects usually occur within 2–10 minutes. Common side effects of sublingual nitrate administration are headaches, dizziness, hot flushing and nausea. Contraindications for the use of GTN include aortic stenosis, hypertrophic cardiomyopathy, systemic hypotension and co-administration with phosphodiesterase-5 inhibitors (eg sildenafil). GTN is recommended for all patients with stable angina, unless contraindicated. When prescribing GTN, patients should be given advice regarding how and when to use GTN and potential side effects that they may experience. They should be advised to inform their doctor if the symptoms are not controlled. GTN can also be useful in preventing episodes of exertional angina when used prior to undertaking physical exertion.
* First-line anti-anginal drugs
* β-adrenergic receptor blockers (beta-blockers) and calcium-channel blockers are considered to be first-line anti-anginal drugs and have been shown in many studies to prevent angina and myocardial ischaemia. The TIBET (Total Ischaemic Burden European Trial) study showed that atenolol produced similar anti-anginal benefits when compared to slow-release nifedipine; no significant additional benefits were seen when the two agents were combined. In the APSIS (Angina Prognosis Study in Stockholm) study, patients with stable angina treated with either metoprolol or verapamil had similar rates of cardiovascular events and mortality. The choice between these two drug classes is generally guided by contraindications, the presence of co-morbidities and patient preference. If one of these agents is not well tolerated, the other can be tried instead. If combination therapy is required, the use of a non-heart-rate limiting dihydropiridine calcium channel blocker (eg amlodipine or slow-release nifedipine) is recommended. The anti-anginal actions of beta-blockers result from a reduction in heart rate, contractility and blood pressure, which result in a reduced myocardial oxygen requirements. Also, by lowering the heart rate, the diastolic component of the cardiac cycle is prolonged, which improves myocardial flow. For maximal efficacy, long-acting, cardioselective beta-blockers that have no intrinsic sympathomimetic activity are preferred. The dose should be titrated to achieve a target resting heart rate of 50–60 beats per minute. The prognostic benefit of beta-blockers in angina has been extrapolated from studies of post myocardial infarction but has not yet been documented in stable angina.
* The potential benefits of beta-blocker therapy are often limited by side effects and contraindications. Among the most common side effects of beta-blockers are fatigue, dizziness, syncope, bronchospam, hyperglycaemia, depression and erectile dysfunction. These agents are contraindicated in patients with reactive airway diseases, severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension, acute heart failure and peripheral vascular disease. Beta-blockers are not generally used in patients with vasospastic angina because of the possibility that unopposed α-adrenergic receptors might have unwanted effects. Abrupt withdrawal of beta-blockers can cause rebound myocardial ischaemia.
* Calcium channel blockers act on L-type Ca2+ receptors and lead to systemic and coronary vasodilatation, reducing afterload and improving myocardial blood flow. Like beta-blockers, non-dihydropyridines (eg verapamil and diltiazem) have additional anti-anginal affects through reductions in heart rate and contractility. Long-acting preparations are preferred. Common side effects of blockers include dizziness, headache, fatigue, flushing, abdominal pain, nausea and peripheral oedema. Like beta-blockers, non-diydropyridine calcium channel blockers are contraindicated by severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension and acute heart failure.
* Second-line anti-angina therapies
* For patients whose symptoms are not well controlled by beta-blockers and calcium-channel blockers, or if contraindications exist for these agents, several options supported by NICE guidelines are available. These include: vasodilators such as long-acting nitrates and nicorandil, a drug that selectively slows the heart rate; ivabradine, and ranolazine, an agent that acts on the fast sodium current to improve cardiac metabolism. When and in which order these second-line agents are used in clinical practice is based on several variables, including pathogenic mechanisms, patient characteristics and co-morbidities, drug interactions and patient preference.
* Long-acting nitrates
* Although there is no evidence that nitrates improve patient prognosis, long-acting nitrates (eg isosorbide mononitrate or isosorbide dinitrate) have been shown to reduce the frequency and severity of angina attacks in patients with stable angina when given alone or in combination with first-line anti-anginal agents. The mechanisms of action, side effects and contraindications for these drugs are similar to those described under sublingual nitrates above. The development of nitrate tolerance and the adverse effects of long-acting nitrates reported recently require consideration before these drugs are prescribed for a given patient.
* Nicorandil
* Nicorandil acts as both a nitric oxide donor and a sarcolemmal K+-adenosine triphosphate (K-ATP)-dependant channel opener, causing K+ efflux and subsequent hyperpolarisation and inhibition of L-type Ca2+ channels, leading to systemic and coronary vasodilatation. The beneficial effects of nicorandil monotherapy are similar to those of metoprolol, amlodipine, diltiazem and nitrates.[20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R20)–[23](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R23) In the IONA (Impact Of Nicorandil in Angina) study, a reduced rate of fatal and non-fatal myocardial infarction and reduced admission for cardiac chest pain were seen in patients taking nicorandil in addition to other standard anti-anginal therapies. The cardio-protective properties of nicorandil might be due to ischaemic preconditioning mediated by activation of mitochondrial K-ATP channels. Common side effects of nicorandil are headaches, dizziness, nausea, vomiting and flushing. Metformin might antagonise the effects of nicorandil by closing K-ATP channels  The use of phosphodiesterase-5 inhibitors and nitrates should be avoided by those taking nicorandil because of the risk of profound systemic hypotension.
* Ivabradine
* Ivabradine is a novel selective heart-rate-lowering anti-anginal drug. Ivabradine inhibits I*f* channels, thereby affecting the intrinsic pacemaker cells of the sino-atrial node. When activated by hyperpolarisation in diastolic range voltages and by adrenergically driven increases in cyclic adenosine monophosphate, the I*f* channel, causes an inward Na+/K+ ionic current across the sarcolemma, leading to spontaneous depolarisation of myocytes in the sino-atrial node. Inhibition of the I*f* current lwers the heart rate. Ivabradine is more effective in patients who have increased I*f* channel activity. It does not affect blood pressure, atrio-ventricular node conduction or contractility. On average, ivabradine reduces resting heart rate by 10 beats per minute. Complete I*f* blockade results in a maximum 30–40% reduction in heart rate due to compensation from other populations of pacemaker cells.
* The anti-anginal efficacy of ivabradine has been shown not to be inferior to atenolol and amlodipine in major trials.In the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I*f* inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) trial, lower rates of hospital admission for fatal and non-fatal myocardial infarction and coronary revascularisation were seen with ivabradine compared to placebo in patients with stable angina and heart rate ≥70 beats per minute
* Ivabradine is indicated for patients with stable angina who are in sinus rhythm and cannot tolerate or have contraindications for conventional heart-rate-lowering agents (ie beta-blockers and non-dyhidropyridine calcium channel blockers), and for patients established on conventional monotherapy whose resting heart rate is sub-optimal. Common side effects include visual ‘flashing lights’ that are often mild and transient, headache, dizziness, blurred vision, 1st degree heart block and ventricular extra-systoles. Contraindications are bradycardia, sick-sinus syndrome, heart block, atrial fibrillation, acute myocardial infarction, acute heart failure, hypotension, and renal and hepatic failure. Ivabradine is metabolised by the CYP3A4 liver enzymes, and significant interactions might occur with drugs that interfere with these enzymes (eg azole anti-fungals, diltiazem, verapamil, macrolide antibiotics and grapefruit juice). Ivabradine can be used safely in patients with asthma and chronic obstructive pulmonary disease.
* Ranolazine
* Ranolazine is a piperazine derivative that is thought to exert its anti-anginal effect by inhibiting ischaemic-induced late inward Na+ currents, preventing Ca2+ overload and reducing diastolic wall tension and extrinsic coronary artery compression.[32](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R32) It might also improve endothelial-mediated coronary vasodilatation.[33](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R33) It was originally thought to act as an anti-metabolic drug, but the concentration required to inhibit myocardial fatty-acid oxidation is much higher than the therapeutic levels used to treat angina.[32](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R32) An advantage of ranolazine is that it does not cause significant haemodynamic changes, with on average less than 2 beats per minute reduction in heart rate and less than 3 mmHg decrease in systolic blood pressure. It is, however, associated with a dose-dependant increase in QT-interval.[25](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R25)
* The clinical efficacy of ranolazine in chronic stable angina as monotherapy and in combination with other anti-anginal drugs has been shown in MARISA (Monotherapy Assessment of Ranolazine in Stable Angina),[34](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R34) CARISA (Combination Assessment of Ranolazine In Stable Angina)[34](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R34) and ERICA (Efficacy of Ranolazine in Chronic Angina) trials. No reduction in cardiovascular death, acute myocardial infarction or recurrent ischaemia was seen in the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes) trial when ranolazine was taken instead of placebo.
* Common side effects of ranolazine are dizziness, nausea, constipation, abdominal pain and headaches. Contraindications to ranolazine are prolonged QT-interval and co-administration with other QT-prolonging drugs, previous history of ventricular tachycardia, and moderate to severe renal impairment or severe hepatic failure. Ranolazine is metabolised by liver CYP3A4 and to a lesser extent by CYP2D6 enzymes, consequently there is a potential for drug interactions. Ranolazine is also a weak inhibitor of cytochrome p450 enzymes and therefore doses of P-glycoprotein substrates (eg simvasatin and digoxin) might need to be reduced for those taking ranolazine.
* Other anti-anginal drugs
* A number of other anti-anginal drugs exist. These are not currently included in NICE guidance, but could in future become available for use in the UK. Trimetazedine, a thiolase that efficiently inhibits beta-oxidation of fatty acids in the myocardium, shifting cardiac metabolism towards more efficient pathways, is used in many European countries as a metabolic modulator.[38](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R38) Angiotensin-converting-enzyme inhibitors are not strictly speaking anti-anginal agents but they have been shown to improve prognosis in patients with diabetes or heart failure and following a myocardial infarction. They are therefore indicated in those circumstances and studies are required to determine their true role in stable angina pectoris.
* F 15845 (3-(R)-[3-(2-methoxyphenylthio-2-(S)-methylpropyl]amino-3,4-dihydro-2H-1,5-benzoxathiepine bromhydrate) is a newly described selective inhibitor of the persistent Na+ current, which has shown anti-ischaemic properties and an ability to prevent ischaemia-induced arrhythmias in animal models; it currently is being assessed in phase II clinical trials.
* Individual approach to anti-anginal drug selection
* In many patients, multiple drugs with different mechanisms of action might be necessary for successful symptom control. Many patients, however, are unable to tolerate conventional angina therapies, mainly those eliciting haemodynamic side effects. The NICE guideline recommends adding a third drug only when two anti-anginal drugs do not satisfactorily control symptoms and the patient is awaiting revascularisation, or in patients for whom revascularisation is not appropriate.[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R4)
* For patients with previous myocardial infarction or heart failure, beta-blockers are the preferred first-line agent because of their proven prognostic benefit.Rate-limiting calcium channel blockers can also improve prognosis in post-myocardial-infarction patients who do not have heart failure.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R5) Calcium channel blockers are preferred in patients with angina who require good hypertensive control. Long-acting nitrates are a logical choice for patients whose symptoms persist despite their taking beta-blockers or calcium channel blockers but who tolerate short-acting nitrates. As nitrates do not improve prognosis, however nicorandil might provide similar anti-anginal effects but with added cardio-protective benefit.
* For patients who develop hypotension or other haemodynamic side effects with conventional anti-anginal therapies, ivabradine and ranolazine are suitable options as they do not exert vasoactive actions. Ivabradine controls heart rate efficiently without significantly causing haemodynamic effects and can be used safely by patients with obstructive airways disease. Ivabradine can also be used in combination with beta-blockers. In the ASSOCIATE (Antianginal efficacy and Safety of the aSsociation Of the I*f* Current Inhibitor ivAbradine with a beTa-blockEr) trial, the combination of ivabradine and atenolol was effective and well tolerated in patients with stable angina, and it was not associated with untoward effects.[42](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R42) Ivabradine has also been shown to reduce cardiovascular death and hospital admission in patients with systolic heart failure.[43](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873712/#R43) In patients with diabetes, ranolazine has an added metabolic benefit in that it has been associated with a significant reduction in HbA1c concentrations.
* It is important to remember that angina results from the interplay of a number of complex vascular and metabolic mechanisms and does not result solely from the presence of obstructive epicardial CAD. Anti-anginal regimes should be, as much as possible, aimed at addressing the prevailing underlying pathophysiological mechanisms in the individual patient. This is particularly important for patients who have chest pain, objective documentation of myocardial ischaemia and angiographically ‘normal’ coronary arteries, in whom coronary microvascular dysfunction and distal epicardial vasoconstriction often play an import role. Calcium channel blockers and other vasodilator agents are useful to these individuals. In patients with true vasospastic angina, ie Prinzmetal's variant angina, calcium channel blockers (usually at high doses) are the best treatment option and are preferred over nitrates for long-term control of symptoms, albeit nitrates (particularly sublingual GTN) can also play an important role in management.
* Conclusions and future directions
* Medical management of stable angina includes lifestyle modification and optimal medical therapy, which encompasses both aggressive pharmacological control of the cardiovascular and metabolic risk profiles, and individualised anti-anginal drug regimes, targeted at specific underlying pathogenic mechanisms. Medical treatment should be regarded as the most important initial intervention and as such should be implemented for all patients as it might reduce the need for invasive coronary intervention, particularly for patients with mild to moderate CAD in whom the prognostic benefit of revascularisation remains unproven.
* Recent advances in the pharmacological management of chronic stable angina offer more precise and individualised solutions. Drug selection can be tailored to the individual on the basis of their underlying pathophysiological mechanisms, which often can be identified from the clinical history. The main aims of therapy remain to control symptoms, thereby improving quality of life, and ultimately to prevent progression of the underlying atherosclerotic coronary heart disease and its long-term complications. For the future, angiogenic gene therapy, using genes that encode vascular endothelial growth factors and fibroblast growth factors, and intramyocardial hematopoietic stem cell therapy are currently being developed. At present and in theory, these offer reasonable promise.
* Q4 .Differentiate between primary and secondary hypertension
* ANS ) OVERVIEW :
* Secondary hypertension (secondary high blood pressure) is high blood pressure that's caused by another medical condition. Secondary hypertension can be caused by conditions that affect your kidneys, arteries, heart or endocrine system. Secondary hypertension can also occur during pregnancy.
* Symptoms
* Like primary hypertension, secondary hypertension usually has no specific signs or symptoms, even if your blood pressure has reached dangerously high levels.
* If you've been diagnosed with high blood pressure, having any of these signs may mean your condition is secondary hypertension:
* High blood pressure that doesn't respond to blood pressure medications (resistant hypertension)
* Very high blood pressure — systolic blood pressure over 180 millimeters of mercury (mm Hg) or diastolic blood pressure over 120 mm Hg
* High blood pressure that no longer responds to medication that previously controlled your blood pressure
* Sudden-onset high blood pressure before age 30 or after age 55
* No family history of high blood pressure
* No obesity
* **When to see a doctor :**
* If you have a condition that can cause secondary hypertension, you may need your blood pressure checked more frequently. Ask your doctor how often to have your blood pressure checked
* Causes
* A number of conditions can cause secondary hypertension. Several kidney diseases may cause secondary hypertension, including:
* **Diabetes complications (diabetic nephropathy).** Diabetes can damage your kidneys' filtering system, which can lead to high blood pressure.
* **Polycystic kidney disease.** In this inherited condition, cysts in your kidneys prevent the kidneys from working normally and can raise blood pressure.
* **Glomerular disease.** Your kidneys filter waste and sodium using microscopic-sized filters called glomeruli that can sometimes become swollen. If the swollen glomeruli can't work normally, you may develop high blood pressure.
* **Renovascular hypertension.** This type of hypertension is caused by narrowing (stenosis) of one or both arteries leading to your kidneys.
* Renovascular hypertension is often caused by the same type of fatty plaques that can damage your coronary arteries (atherosclerosis) or a separate condition in which the muscle and fibrous tissues of the renal artery wall thicken and harden into rings (fibromuscular dysplasia). This condition can cause irreversible kidney damage.
* Medical conditions affecting hormone levels may also cause secondary hypertension. These conditions may include:
* **Cushing syndrome.** In this condition, corticosteroid medications may cause secondary hypertension, or hypertension may be caused by a pituitary tumor or other factors that cause the adrenal glands to produce too much of the hormone cortisol.
* **Aldosteronism.** In this condition, a tumor in one or both of the adrenal glands, increased growth of normal cells in one or both of the adrenal glands or other factors cause the adrenal glands to release an excessive amount of the hormone aldosterone. This makes your kidneys retain salt and water and lose too much potassium, which raises blood pressure.
* **Pheochromocytoma.** This rare tumor, usually found in an adrenal gland, increases production of the hormones adrenaline and noradrenaline, which can lead to long-term high blood pressure or short-term spikes in blood pressure.
* **Thyroid problems.** When the thyroid gland doesn't produce enough thyroid hormone (hypothyroidism) or produces too much thyroid hormone (hyperthyroidism), high blood pressure can result.
* **Hyperparathyroidism.** The parathyroid glands regulate levels of calcium and phosphorus in your body. If the glands secrete too much parathyroid hormone, the amount of calcium in your blood rises — which triggers a rise in blood pressure.
* Other possible causes of secondary hypertension include:
* **Coarctation of the aorta.** With this defect that's generally present at birth, the body's main artery (aorta) is narrowed (coarctation). This forces the heart to pump harder to get blood through the aorta and to the rest of your body. This, in turn, raises blood pressure — particularly in your arms.
* **Sleep apnea.** In this condition, often marked by severe snoring, breathing repeatedly stops and starts during sleep, causing you to not get enough oxygen.
* Not getting enough oxygen may damage the lining of the blood vessel walls, which may make your blood vessels less effective in regulating your blood pressure. In addition, sleep apnea causes part of the nervous system to be overactive and release certain chemicals that increase blood pressure.
* **Obesity.** As you gain weight, the amount of blood circulating through your body increases. This puts added pressure on your artery walls, increasing your blood pressure.
* Excess weight often is associated with an increase in heart rate and a reduction in the capacity of your blood vessels to transport blood. In addition, fat deposits can release chemicals that raise blood pressure. All of these factors can cause hypertension.
* **Pregnancy.** Pregnancy can make existing high blood pressure worse, or may cause high blood pressure to develop (pregnancy-induced hypertension or preeclampsia).
* **Medications and supplements.** Various prescription medications — such as pain relievers, birth control pills, antidepressants and drugs used after organ transplants — can cause or aggravate high blood pressure in some people.
* Over-the-counter decongestants and certain herbal supplements, including ginseng, licorice and ephedra (ma-huang), may have the same effect. Many illegal drugs, such as cocaine and methamphetamine, also increase blood pressure.
* Risk factors
* The greatest risk factor for having secondary hypertension is having a medical condition that can cause high blood pressure, such as kidney, artery, heart or endocrine system problems.
* Complications
* Secondary hypertension can worsen the underlying medical condition you have that's causing your high blood pressure. If you don't receive treatment, secondary hypertension can also be associated with other medical conditions, such as:
* **Damage to your arteries.** This can result in hardening and thickening of the arteries (atherosclerosis), which can lead to a heart attack, stroke or other complications.
* **Aneurysm.** Increased blood pressure can cause your blood vessels to weaken and bulge, forming an aneurysm. If an aneurysm ruptures, it can be life-threatening.
* **Heart failure.** To pump blood against the higher pressure in your vessels, your heart muscle thickens. Eventually, the thickened muscle may have a hard time pumping enough blood to meet your body's needs, which can lead to heart failure.
* **Weakened and narrowed blood vessels in your kidneys.** This can prevent these organs from functioning normally.
* **Thickened, narrowed or torn blood vessels in the eyes.** This can result in vision loss.
* **Metabolic syndrome.** This syndrome is a cluster of disorders of your body's metabolism — including increased waist circumference, high triglycerides, low high-density lipoprotein (HDL) cholesterol (the "good" cholesterol), high blood pressure and high insulin levels.
* If you have high blood pressure, you're more likely to have other components of metabolic syndrome. The more components you have, the greater your risk of developing diabetes, heart disease or stroke.
* **Trouble with memory or understanding.** Uncontrolled high blood pressure also may affect your ability to think, remember and learn. Trouble with memory or understanding concepts is more common in people who have high blood pressure.
* Secondary hypertension differs from the usual type of high blood pressure (primary hypertension or essential hypertension), which is often referred to simply as high blood pressure. Primary hypertension has no clear cause and is thought to be linked to genetics, poor diet, lack of exercise and obesity.
* Proper treatment of secondary hypertension can often control both the underlying condition and the high blood pressure, which reduces the risk of serious complications — including heart disease, kidney failure and strokes.
* (a)Explain the effect of renin on hypertension
* Ans )
* To determine whether the elevated plasma renin activity in some cases of mild essential hypertension expresses sympathetic-nervous-system overactivity, we compared indexes of sympathetic activity in 16 patients with mild high-renin essential hypertension, 15 hypertensive patients with normal plasma renin activity and 20 normal subjects. Patients with elevated activity exhibited a raised plasma norepinephrine concentration (P<0.05), a greater fall in cardiac output with cardiac beta-adrenergic blockade by intravenous propranolol (P<0.01), reduction in total peripheral vascular resistance with alpha-adrenergic blockade produced by intravenous phentolamine (P<0.01), and reduction to normal of blood pressure by "total" autonomic blockade (atropine, propranolol and phentolamine). On psychometric testing, patients with high-renin hypertension, but not those with normal plasma renin activity, exhibited suppressed hostility (P<0.01), a behavioral pattern linked to increased sympathetic activity. The hypertension in these patients with high renin activity is neurogenic and possibly psychosomatic in origin.
* (b)What is the importance of pharmacological treatment of hypertension
* Ans )
* Hypertension is one of the most important preventable causes of premature death worldwide,[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B1) and the benefits of antihypertensive drugs have been confirmed by the largest evidence base from clinical trials in medicine. Many classes of drugs are available for treatment, and debate has raged about whether the benefits of treatment are purely a function of the quality of blood pressure control or whether the type of drug used might also be a powerful determinant of outcome. This is a key question because the difference in cost between “older” drugs (thiazides or β blockers) and “newer” drugs (such as angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers) is substantial. A meta-analysis of trials of treatment for hypertension with the newer drugs found that ACE inhibitors and calcium channel blockers were likely to reduce cardiovascular morbidity and mortality by the same order of magnitude as β blockers or thiazides,[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B2) but such analyses have insufficient statistical power to detect cause specific outcomes with regard to specific drugs.
* Recently, the “antihypertensive and lipid lowering to prevent heart attack trial” (ALLHAT)—the largest ever randomised trial of antihypertensive treatment—reported its results.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B3) It was designed to determine whether the choice of first line treatment for hypertension influenced cardiovascular outcome. Importantly, the trial was sufficiently large to examine cause specific outcomes and was the first hypertension study to have sufficient power to examine the combined incidence of fatal coronary heart disease and non-fatal myocardial infarction as the primary end point.
* ALLHAT was a randomised double blind controlled clinical trial conducted in 623 centres in North America. The trial randomised 42 418 patients with mild to moderate hypertension aged 55 years or older (mean age 67 years) with one additional cardiovascular risk factor to one of four antihypertensive treatments: the diuretic chlorthalidone (12.5-25 mg daily), the ACE inhibitor lisinopril (10-40 mg daily), the calcium channel blocker amlodipine (2.5-10 mg daily), or the α blocker doxazosin (1-8 mg daily). The doxazosin arm was stopped prematurely in 2000 after a reported excess of cardiovascular events (principally congestive heart failure) compared with the reference drug, chlorthalidone.[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B4) This left 33 357 patients who completed the trial for a mean follow up of 4.9 years.
* The design of the trial ensured the inclusion of large numbers of patients' groups, previously under-represented in trials of blood pressure—notably women (15 658, 47%), black Americans (10 702, 35%), Hispanics (5246, 19%), and people with diabetes mellitus (12 063, 36%). The primary outcome occurred in 2956 participants, and no differences were found between the rates with the reference drug chlorthalidone (11.5%), and amlodipine (11.3%) and lisinopril (11.4%). Moreover, this conclusion is valid irrespective of the patient's sex, ethnicity, or the presence or absence of diabetes. Four major secondary end points were prespecified—all cause mortality, fatal and non-fatal stroke, combined coronary heart disease, and combined cardiovascular disease No difference was found between chlorthalidone and amlodipine for any of these major secondary end points. No difference was found between lisinopril and chlorthalidone for two of the secondary end points (all cause mortality or combined coronary heart disease). However, lisinopril was significantly less effective than the diuretic at reducing the other two secondary end points—stroke and combined cardiovascular disease.
* Heart failure was diagnosed significantly more often over six years in patients randomised to either amlodipine (more by 38%) or lisinopril (19%) compared with chlorthalidone. This finding must be viewed with caution. It should be emphasised that this was not a primary or major secondary end point of the study and it was not well validated. It is not surprising that patients randomised to diuretic got less oedema than those randomised to ACE inhibitor or calcium channel blocker. Moreover, from a clinical perspective it is not a major finding in that patients with hypertension similar to those randomised in this trial (aged ≥55 years, mean age 67 years) would receive a diuretic as part of their treatment.
* What does this new information tell us about the drug treatment of hypertension? This trial reaffirms current recommendations that a thiazide diuretic is at least as effective as a first line treatment as more expensive alternatives in an older population with hypertension.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B5) Importantly, this also applies to people with diabetes mellitus in whom doctors have been reluctant to prescribe thiazide diuretics, a reluctance that is no longer justified. The new information also dismisses previous concerns about the safety and efficacy of calcium channel blockers for the treatment of hypertension.[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B6) This sends out an important and powerful message to those who generate and publish unsound conclusions from small studies, post hoc analyses, and observational data. Such observations are usually sensational, often wrong, and they have the potential to do much harm to patients—there is no substitute for a large randomised clinical trial for the formulation of healthcare policy.
* The halo of ACE inhibition has been dented by this trial. There was no evidence of the much touted benefits of ACE inhibition “independent of blood pressure” in terms of protection against cardiovascular disease and stroke. It is well recognised that older people and black people respond less well to ACE inhibition with regard to reduction of blood pressure than younger people and white people because their renin-angiotensin systems are more suppressed. Blood pressure was less well controlled in patients randomised to lisinopril throughout the trial, especially in black patients. Small differences in blood pressure (2-4 mm Hg) in large clinical studies can have a major impact on outcome and are the most likely explanation for the reduced protection against stroke and cardiovascular disease with ACE inhibition in this trial. But this is a double edged sword, and the same argument must also apply to explain the benefit when similarly small blood pressure differences occurred in favour of ACE inhibition compared with placebo in studies such as HOPE.[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B8) Such small blood pressure differences can no longer be dismissed as unimportant or irrelevant to clinical outcomes.[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B9)
* When ALLHAT was designed in the early 1990s much debate arose about the need to define first line treatment for hypertension. This has become less relevant in clinical practice as trials continue to confirm that most patients require more than one drug to control blood pressure. This was also confirmed in this trial, which showed that 63% of patients required two or more drugs to control blood pressure to less than 140/90 mm Hg. Moreover, blood pressure control was more difficult in patients at highest risk—older patients, patients with highest systolic blood pressure at baseline, black patients, or diabetic patients—who generally require more than two drugs.[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125015/#B10) ALLHAT does not give information about the ideal combination of drugs required to achieve optimal blood pressure targets. One cannot conclude that the combination of a diuretic with a newer drug would not be more effective than a diuretic and β blocker combination at reducing blood pressure, morbidity, and mortality.
* The key message from this trial is that what matters most is getting blood pressure controlled, and that this is overwhelmingly more important than the means. Combinations of several drugs will be required for most patients, and such an antihypertensive treatment cocktail should include a thiazide diuretic. ALLHAT perhaps heralds the end of an era of initial treatment comparisons for hypertension and points to a new need for “real world research.” In managing hypertension we have a range of effective and safe drugs and a robust evidence base for treatment. But if patients are to benefit from this trial, and all before it, we now need to define the best way of implementing the evidence in clinical practice.
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* (B) EMERGENCY MEDICINE THAT CAN BE USED ;
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| * (A) PATHWAY OF TREATMENT OF HYPERTENSION : |  |  |
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* Differentiate between right heart failure and left heart failure ?
* ANS)
* INTRODUCTION :
* In heart failure, the heart can no longer pump enough blood around the body. The heart muscle is either too weak or not elastic enough. Different parts of the heart may be affected too. The type of medication people use for the treatment of heart failure will depend on the type of heart failure they have.
* Heart failure often only affects the left or right side of the heart, but can affect both. Doctors differentiate between three types of heart failure, accordingly:
* Left-sided heart failure: The left ventricle of the heart no longer pumps enough blood around the body. As a result, blood builds up in the pulmonary veins (the blood vessels that carry blood away from the lungs). This causes shortness of breath, trouble breathing or coughing – especially during physical activity. Left-sided heart failure is the most common type.
* Right-sided heart failure: Here the right ventricle of the heart is too weak to pump enough blood to the lungs. This causes blood to build up in the veins (the blood vessels that carry blood from the organs and tissue back to the heart). The increased pressure inside the veins can push fluid out of the veins into surrounding tissue. This leads to a build-up of fluid in the legs, or less commonly in the genital area, organs or the abdomen (belly).
* Biventricular heart failure: In biventricular heart failure, both sides of the heart are affected. This can cause the same symptoms as both left-sided and right-sided heart failure, such as shortness of breath and a build-up of fluid.
* Left-sided heart failure is usually caused by coronary artery disease (CAD), a heart attack or long-term high blood pressure. Right-sided heart failure generally develops as a result of advanced left-sided heart failure, and is then treated in the same way. It is sometimes caused by high blood pressure in the lungs, an embolism in the lungs (pulmonary embolism), or certain lung diseases such as [COPD](https://www.ncbi.nlm.nih.gov/books/n/pmh_iqwig/glossary/def-item/def302/).
* Classification based on pumping ability
* Nowadays, heart failure is increasingly being classified based on the pumping ability of the heart. This is because the pumping ability plays an important role when choosing the most suitable medication. There are two types of heart failure here:
* Heart failure with reduced pumping ability: The heart muscle has become weaker, and no longer pumps enough blood around the body when it contracts (squeezes). As a result, the organs in the body don’t get enough oxygen. The medical term for this is “heart failure with reduced ejection fraction.”
* Heart failure with preserved pumping ability: Although the heart muscle is still strong, it can no longer relax and widen enough after it has squeezed blood out, so it doesn’t fill up with blood properly. Despite pumping strongly enough, not enough blood is pumped out into the body as a result, especially during physically strenuous activities. Doctors call this “heart failure with preserved ejection fraction.”
* Heart failure with reduced pumping ability is sometimes referred to as “systolic” heart failure, and heart failure with preserved pumping ability is also known as “diastolic” heart failure. The systolic phase of the cardiac cycle is the phase when the heart contracts (squeezes), and the diastolic phase is when the heart relaxes and widens.
* Classification based on course of the disease
* Heart failure can develop suddenly, for instance after a heart attack or due to certain heart rhythm problems. This is known as acute heart failure.
* But it usually develops gradually over time as a result of a different medical problem, such as permanently high blood pressure. This is known as chronic heart failure.
* 
* Summarize the pharmacotherapy of heart failure ?
* ANS)
* INTRODUCTION
* Heart failure (HF) affects more than 6.5 million people in the United States and has a 50% mortality rate within five years of diagnosis. The lifetime risk of HF at 45 years of age is 30% for white men and 32% for white women. HF is a progressive disease that can result from any structural or functional changes of the heart, leading to the impairment of ventricular filling or ejection of blood. As a consequence, the heart cannot pump blood fast enough to meet the demands of the body.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b3-ptj4207464) Typical symptoms of HF include dyspnea and fatigue. The symptoms that present are usually nonspecific to HF but can lead to the review of more specific signs, such as elevated jugular venous pressure or displacement of the apical impulse, and can guide a practitioner to review radiological data consistent with HF.
* Imaging plays an important role in the diagnosis of HF, with echocardiography being the gold standard. Transthoracic echocardiography is the method of choice for assessment of myocardial systolic and diastolic function of both the left and right ventricles. Once the diagnosis is confirmed, the goals of treatment are to improve clinical status, functional capacity, and quality of life; to prevent hospital admission; and to reduce mortality.
* The 2013 guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) defined two types of HF: preserved ejection fraction (HF*p*EF) and reduced ejection fraction (HF*r*EF). A preserved ejection fraction (EF) is 50% or greater, while reduced EF was defined as 40% or less. Patients with an EF of more than 40% but less than 50% represent an intermediate group whose treatment is similar to HF*p*EF.In addition to HF type, patients can be assigned a class and/or stage of HF. The New York Heart Association (NYHA) defines four classes of HF:
* Class I: No physical limitation; ordinary physical activity does not cause HF symptoms
* Class II: No symptoms at rest, but ordinary physical activities cause HF symptoms
* Class III: No symptoms at rest, but less-than-ordinary physical activities cause HF symptoms
* Class IV: Symptoms of HF at rest
* The ACCF/AHA also defines four stages of HF:
* Stage A: At high risk for HF but without structural heart disease or symptoms of HF
* Stage B: Structural heart disease but without signs or symptoms of HF
* Stage C: Structural heart disease with prior or current symptoms of HF
* Stage D: Refractory HF requiring specialized interventions
* The NYHA classes focus on exercise capacity and the symptomatic status of the disease, whereas the ACCF/AHA stages evaluate the development and progression of the disease.
* After a patient has been diagnosed with a type, stage, and class, treatment can be determined. First-line drug therapy for all patients with HF*r*EF should include an angiotensin-converting enzyme (ACE) inhibitor and beta blocker.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b5-ptj4207464) These medications have been shown to decrease morbidity and mortality.
* However, the 2016 “Focused Update on New Pharmacological Therapy for Heart Failure” from the ACCF, AHA, and Heart Failure Society of America (HFSA) changed how patients are managed in stage C with HF*r*EF. The new guidelines focused on two new classes of medications: an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan/sacubitril [Entresto, Novartis]) and a sinoatrial node modulator (ivabradine [Corlanor, Amgen]). A recent study found valsartan/sacubitril to be superior to the ACE inhibitor enalapril when added to standard therapy, including a beta blocker and diuretics, in reducing the risk of death and hospitalization.Ivabradine also reduced the risk of hospitalization for worsening heart failure and the risk of cardiovascular death.
* ACE INHIBITOR
* The ability of ACE inhibitors, such as enalapril and lisinopril, to reduce mortality when taken concurrently with other HF*r*EF medications has made this class of medications the mainstay for treatment of HF*r*EF in patients free from any contraindications to their use
* ACE inhibitors decrease peripheral resistance and reduce the load on the failing myocardium by inhibiting the conversion of angiotensin I to angiotensin II, thus preventing vasoconstriction and causing relaxation of the vasculature. The efficacy of ACE inhibitors has been proven over several decades. Major trials analyzing ACE inhibitors in HF*r*EF have utilized them in addition to standards of care such as digoxin, vasodilators, loop diuretics, potassium-sparing diuretics, and beta blockers. The CONSENSUS trial, which compared enalapril with placebo in addition to standard of care, showed that enalapril reduced overall mortality risk by 27% and significantly decreased the number of patients with HF*r*EF progression. The SOLVD trial demonstrated that, compared with placebo, treatment with enalapril over the course of three years prevented 50 premature deaths and 350 hospitalizations per 1,000 patients. Collectively, these trials suggest that ACE inhibitors, when taken concurrently with other HF*r*EF medications, provide significant reductions in morbidity and mortality. These benefits have been shown to remain clinically significant throughout long courses of therapy.
* Contraindications to ACE inhibitor therapy include hypersensitivity, previous angioedema from ACE inhibitor use, or concomitant use with aliskiren. Adverse effects to monitor for in patients using ACE inhibitors include headache, cough, diarrhea, dizziness, and fatigue; most of these effects are transient and mild. More serious events include reversible increases in serum creatinine (SCr) and symptomatic hypotension, both related to the hemodynamic effects of ACE inhibitors. While the exact number is not agreed upon, an SCr increase of up to 30% is regarded as acceptable and does not warrant stopping ACE inhibitor therapy. In trials, small but significant increases in serum potassium were observed. Caution should be exercised in patients with pre-existing hypotension, those with baseline hyperkalemia (potassium greater than 5 mEq/L), and those receiving concomitant potassium supplements or potassium-sparing diuretics.
* The usual dosing strategy for ACE inhibitors is to initiate at a low dose and double the dose every one to two weeks, if tolerated, up to the prespecified target dose .Monitor patients for hypotension, potassium levels, and decreased renal function during the titration period to assess tolerability. Patients with pre-existing conditions that put them at a higher risk for side effects (sodium levels less than 130 mEq/L, creatinine clearance [CrCl] less than 30 mL/min, an increase in diuretic dose in the past week, or treatment with a potassium-sparing diuretic) may be initiated at a lower dose.
* ANGIOTENSIN RECEPTOR BLOCKERS
* Angiotensin receptor blockers (ARBs) inhibit the renin–angiotensin–aldosterone system (RAAS) by blocking the binding of angiotensin II to its receptor, which in turn leads to vasoconstriction and prevents the release of aldosterone. Although their mechanism of action is similar to that of ACE inhibitors, ARBs do not cause an inhibition of kininase, which reduces the incidence of cough in comparison with ACE inhibitors. ARBs be used to reduce morbidity and mortality in patients who are intolerant of ACE inhibitors because of cough or angioedema or in patients who are tolerating ARBs for another indication. In addition, the 2016 guidelines recommend that ARBs be used with caution in patients with a history of angioedema with ACE inhibitors because of the risk of cross-reaction. For patients with HF*r*EF NYHA class II or III, the guidelines recommend replacing ARB therapy with an ARNI..
* . The primary outcome of cardiovascular death or hospitalization for HF occurred in 33% of candesartan patients versus 40% of placebo patients (covariate adjusted hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.60–0.81; *P* < 0.001).
* It is important to monitor patients on ARB therapy closely and titrate the dose as tolerated. The Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study evaluated more than 3,800 patients with HF*r*EF NYHA class II–IV who were intolerant of ACE inhibitors; participants were randomly assigned to losartan 150 mg daily or 50 mg daily. The primary endpoint, death or admission for HF, occurred in 43% of patients in the 150-mg group versus 46% of patients in the 50-mg group (HR, 0.90; 95% CI, 0.82–0.99; *P* = 0.027).[20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b20-ptj4207464) This study, although specific to losartan dosing, shows the value of uptitrating ARB dosing for maximal benefit. When initiating ARB therapy, start with a low dose and titrate up as tolerated by doubling the dose to the target.
* Baseline renal function and serum potassium should be established prior to initiating ARB therapy. ARBs can cause hyperkalemia due to the inhibition of aldosterone, often in combination with other predisposing factors such as combination medications or physiological conditions that have reduced serum aldosterone concentrations. It is important to monitor these assays regularly to identify abnormalities because modifications of the patient’s drug therapy or dietary intake of potassium may be required.
* BETA BLOCKERS
* The beneficial effect of beta blockade in HF*r*EF has been documented for more than 40 years. Since 1975, data have shown that the use of bisoprolol, carvedilol, or sustained-release metoprolol succinate reduces morbidity and mortality in patients with HF*r*EF. These are the only beta blockers tested in large clinical trials to show a mortality benefit, which led to their inclusion in the HF guidelines as first-line agents in all patients with HF*r*EF to reduce morbidity and mortality unless contraindicated. These three agents share a common pathway: They all block the β1-adrenergic receptor located on the heart. HF*r*EF stimulates the RAAS and sympathetic system in order to compensate for the reduced EF. However, this activation may accelerate ventricular remodeling. By blocking β1 receptors, these beta blockers prevent ventricular remodeling promoted by the stimulated RAAS and sympathetic system. While metoprolol and bisoprolol are selective for the β1 receptor, carvedilol also blocks the β2 and α1 receptors, leading to vasodilation. The COPERNICUS study had patients double their dose of carvedilol until a mean dose of 37 mg per day was achieved, showing an all-cause mortality of 11.4% versus 18.5% in the placebo group (*P* = 0.00013). Bisoprolol was evaluated in the CIBIS-II trial, leading to all-cause mortality of 8.8% versus 13.2% in the placebo group (*P* < 0.0001). Finally, the MERIT-HF trial compared metoprolol succinate with placebo in patients on baseline ACE-inhibitor and diuretic therapy to evaluate all-cause mortality (7.2% versus 11%; *P* = 0.00009) and all-cause mortality plus all-cause hospitalization (32% versus 38%; *P* < 0.001).[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b4-ptj4207464),[25](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b25-ptj4207464)
* Beta blockers should be initiated at low doses and titrated slowly to target doses if tolerable . Adverse events include fluid retention and worsening HF*r*EF, fatigue, bradycardia or heart block, and hypotension. The fluid retention or worsening HF*r*EF associated with beta blockers do not generally warrant the permanent withdrawal of treatment. Beta-blocker-induced bradycardia is generally asymptomatic and thus requires no treatment; however, if the bradycardia is accompanied by dizziness, lightheadedness, or second- or third-degree heart block, the dose of the beta blocker should be decreased. Patients should be monitored closely for changes in vital signs and symptoms during this titration period. If the target doses are not tolerated, the highest tolerated dose should be continued.
* ALDOSTERONE ANTAGONISTS
* Aldosterone receptor antagonists (also called mineralocorticoid receptor antagonists [MRAs]) are recommended for NYHA class II–IV HF patients with an EF of 35% or less, glomerular filtration rate of at least 30 mL/min/1.73 m2, and a potassium level of 5.0 mEq/dL or lower.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b3-ptj4207464) Studies have demonstrated that aldosterone receptor antagonists (when given in conjunction with ACE inhibitors and beta blockers) reduce the risk of morbidity and mortality in patients with NYHA class III–IV HF*r*EF with an EF of 35% or less. Further studies found similar benefits in NYHA class II HF*r*EF patients with an EF of 35% or less.
* Two aldosterone receptor antagonists are available in the United States—spironolactone and eplerenone. Spironolactone is a nonselective aldosterone antagonist, while eplerenone is selective to the aldosterone receptor.[30](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b30-ptj4207464),[31](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b31-ptj4207464) Aldosterone is an endogenous steroid hormone that increases sodium retention and facilitates magnesium/potassium loss. Aldosterone may ultimately cause myocardial fibrosis, vascular injury, direct vascular damage, and baroreceptor dysfunction leading to the development and progression of HF*r*EF. The use of MRAs may slow HF progression and prevent or reverse cardiac remodeling and the development of arrhythmias.. Although ACE inhibitors block aldosterone, evidence indicates that this effect is only transient.[36](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b36-ptj4207464) There is little data comparing the efficacy of spironolactone versus eplerenone, but both have proven effective in placebo-controlled trials.. The initial and maximum doses of aldosterone antagonists should be adjusted based on renal function . Spironolactone, which is chemically similar to progesterone, increases peripheral estradiol formation, potentially leading to adverse events, including gynecomastia or amenorrhea. These adverse events are not seen with eplerenone because it is selective to the aldosterone receptor. Furthermore, although ACE inhibitors and aldosterone antagonists are often used concomitantly for patients with H*Fr*EF, concurrent use of these agents can cause life-threatening hyperkalemia. Due to the risk of elevated potassium levels, potassium supplements should be discontinued (or reduced and carefully monitored in those with a history of hypokalemia) when initiating aldosterone antagonist therapy in a patient already receiving an ACE inhibitor. Careful monitoring of potassium levels and renal function should be performed at initiation and closely checked within two to three days and again at seven days after initiation. Patients should subsequently be monitored monthly for the first three months and every three months thereafter. More frequent monitoring may be appropriate for patients who have fluctuating potassium levels, renal function, or fluid status, as well as patients who have had recent changes in their ACE inhibitor/ARB dosing regimens. Additional monitoring parameters include daily measures of blood pressure and weight.
* DIURETICS
* Although no data have shown that they reduce mortality or hospital readmission, diuretics are the only agents that can adequately control the fluid retention associated with HF*r*EF. Unless contraindicated, diuretics are recommended in all HF*r*EF patients with fluid retention to improve symptoms. Diuretic use is generally combined with moderate dietary sodium restriction.
* Loop diuretics, such as furosemide, are the preferred diuretic agents for most HF*r*EF patients. Loop diuretics work at the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption. In comparison, thiazide diuretics are less potent and thus have a less significant effect on fluid retention/edema.. Thiazides work at the renal distal convoluted tubule to inhibit the sodium chloride cotransporter. Due to their antihypertensive effects, thiazide diuretics may be the preferred diuretic agents for HF*r*EF patients with concurrent hypertension and mild fluid retention. Some HF*r*EF patients may remain volume-overloaded despite the use of maximal loop diuretic therapy. Such loop diuretic resistance may be overcome by intravenous administration of loop diuretics or by the addition of a thiazide diuretic.
* Adverse effects of diuretics include fluid depletion, hypotension, azotemia, and depletion of sodium, potassium, magnesium, chloride, and calcium. Typical monitoring parameters for these agents include daily weight and blood pressure measurements, and periodic monitoring of renal function. Because loop and thiazide diuretics may increase uric acid, patients utilizing these agents should be monitored for changes in uric acid levels as well as signs and symptoms of gout. The presence of orthopnea and B-type natriuretic peptide levels should be followed daily if possible during inpatient admissions.
* Diuretic therapy is initiated at low doses and is titrated up as needed and as tolerated. Adequate treatment is not determined by reaching a set target dose, but rather by looking for an increase in urine output and a 0.5-kg to 1.0-kg decrease in daily weight .These clinical markers should be monitored closely to determine appropriate patient-specific diuretic doses.
* VASODILATORS
* Vasodilators have been shown to reduce mortality in patients self-described as African-Americans with NYHA class III–IV HF*r*EF. They are also recommended to reduce morbidity and mortality in patients with current or prior symptomatic HF*r*EF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated. Both hydralazine and isosorbide dinitrate have vasodilatory effects. Isosorbide dinitrate causes a release of nitric oxide that relaxes vascular smooth muscle, affecting both arteries and veins. In comparison, hydralazine works to selectively relax arterial smooth muscle and may minimize nitrate tolerance.
* A 1986 trial demonstrated that the one-year mortality rate for the hydralazine and isosorbide dinitrate treatment group was 38% lower than the placebo control group.[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b9-ptj4207464) Furthermore, a study that analyzed hydralazine and isosorbide dintirate treatment specifically in black patients found a 43% reduction in relative mortality risk and a 33% reduction in first HF*r*EF hospitalization compared with placebo.[45](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b45-ptj4207464) Finally, a study that evaluated racial differences between white and black patients showed that when comparing hydralazine and isosorbide dinitrate therapy with placebo, mortality benefits were seen only in black patients. These results are thought to be due to the increased incidence of hypertension and decreased levels of plasma norepinephrine and renin typically seen in black patients.
* A starting dose of hydralazine 37.5 mg/isosorbide dinitrate 20 mg (available as a combination tablet) three times per day is recommended. When administering hydralazine and isosorbide dinitirate separately, the recommendation is to start with hydralazine 25 mg to 50 mg three or four times per day and isosorbide dinitirate 20 mg to 30 mg three or four times per day. However, the combination tablet will help reduce a patient’s pill burden as well as the possible need to cut hydralazine tablets in half depending on the dose. If the medication is tolerated without major side effects for two weeks, the dose can be doubled. The maximum recommended dose is hydralazine 75 mg/isosorbide dinitrate 40 mg three times per day or hydralazine 300 mg daily in divided doses with isosorbide dinitrate 120 mg daily in divided doses.
* Adverse effects of hydralazine and isosorbide dinitrate include nausea, fatigue, palpitations, joint pain, and rash. A trial comparing the adverse effects of hydralazine and isosorbide dintirate to ACE inhibitors found that headaches were seen more often while symptomatic hypotension and cough were seen less often in the vasodilator combination group than in the ACE inhibitor group. The use of phosphodiesterase-5 inhibitors is contraindicated with nitrates due to the increased risk of adverse events such as symptomatic hypotension
* DIGOXIN
* Digoxin has been shown to decrease the rate of HF*r*EF-related hospitalizations when used in addition to standard of care. Digoxin is a cardiac glycoside that has been used for more than 200 years. It inhibits the sodium–potassium ATPase pump, causing positive inotropy (increasing force and velocity of myocardial contraction) and deactivating neurohormonal effects (decreasing sympathetic and RAAS responses)
* Despite extensive use of digoxin, its role and utility in chronic HF have been controversial. However, various studies have elucidated the effects of digoxin on morbidity and mortality in HF*r*EF patients. HF*r*EF patients on digoxin who were switched to placebo showed a significant worsening of HF compared with those who continued to receive digoxin therapy (relative risk, 5.9; *P* < 0.001).. Symptom severity, as measured by exercise tolerance, showed worsening maximal exercise capacity in patients receiving placebo compared with digoxin therapy (4.5-second change in exercise time; *P* = 0.003). However, digoxin did not demonstrate a mortality benefit in patients with HF*r*EF or HF*p*EF. A majority of patients included in these trials were on an ACE inhibitor, a beta blocker, and/or a diuretic at baseline.
* The many adverse effects of digoxin are generally dose dependent and are far less likely when the drug is used in the recommended dosage range. However, less commonly, cardiac toxicity, including heart block, may be seen in the therapeutic range, especially if patients have hypokalemia, hypomagnesemia, or hypothyroidism. Digoxin toxicity typically presents with the combination of cardiac effects and dose-dependent central nervous system effects (visual changes, anxiety, dizziness, etc.) or gastrointestinal effects (anorexia, nausea, vomiting, and abdominal pain). Serum trough levels may be monitored to minimize adverse effects. The target trough range for HF*r*EF patients is 0.4 ng/mL to 0.9 ng/mL.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b3-ptj4207464) The initial dose of digoxin is typically 0.125 mg to 0.250 mg daily with no need for a loading dose. Patients who are elderly, have poor renal function, or have low lean body mass should start with 0.125 mg daily or every other day.
* IVABRADINE
* Ivabradine is a heart-rate–reducing agent approved in the U.S. in 2015 for use in patients with HF*r*EF. It is indicated in patients with stable, symptomatic, chronic HF with an EF of 35% or less and a resting heart rate greater than 70 beats per minute (bpm). It is an inhibitor of the “funny current” or I(f) channel. The I(f) channel controls heart rate through modulation of autonomic neurotransmitters, such as epinephrine. Specific blockade of these channels removes the contribution I(f) has on pacemaker depolarization and thus slows the heart rate.
* Ivabradine was evaluated in a randomized, placebo-controlled trial to determine whether lowering a patient’s resting heart rate leads to a reduction in cardiovascular death or hospital admission for worsening HF. At baseline, 89% of the patients randomized to the ivabradine group were taking a beta blocker, 79% were taking an ACE inhibitor, 14% were using an ARB, and 22% were taking cardiac glycosides, such as digoxin. The study enrolled patients who had an EF of less than 35% and were in sinus rhythm with a heart rate of 70 bpm or higher. Twenty-four percent of patients in the ivabradine group versus 29% of patients in the placebo group had a primary endpoint event (HR, 0.82; 95% CI, 0.75–0.90; *P* < 0.0001) A subgroup analysis showed that the effects of ivabradine are related to the patient’s heart rate. Ivabradine significantly reduced the rates of cardiovascular death and HF hospitalizations in patients taking less than 50% of the guideline-recommended beta-blocker dose. However, no significant difference was seen in the primary endpoint among patients taking 50% or more of the recommended beta-blocker dose.
* Ivabradine is typically initiated at 5 mg orally twice daily and is titrated to a target heart rate of 50 bpm to 60 bpm every two weeks. At this time, if the heart rate is greater than 60 bpm, the dose of ivabridine should be increased by 2.5 mg per dose. The maximum dose is 7.5 mg orally twice daily. In comparison, if the heart rate is less than 50 bpm or a patient presents with symptomatic bradycardia, the dose should be decreased by 2.5 mg per dose and discontinued if necessary.
* A significantly higher rate of symptomatic bradycardia, atrial fibrillation, and visual changes occurred in patients receiving ivabradine compared with placebo. Due to these adverse events, this agent should be avoided in patients with resting heart rates less than 60 bpm, low blood pressure, decompensated HF*r*EF, and cardiac conditions, including sick sinus syndrome, sinoatrial block, or third-degree heart block. Due to its hepatic metabolism, ivabradine should be avoided in patients with severe hepatic impairment and with concomitant use of potent cytochrome P450 3A4 inhibitors.
* The 2016 focused update to the 2013 ACCF/AHA guidelines recommends ivabradine use in patients with symptomatic, stable, chronic NYHA class II–III HF*r*EF with an EF of 35% or less who are in sinus rhythm and have a resting heart rate of at least 70 bpm. It is important to titrate beta blockers to their maximally tolerated dose prior to initiation of ivabradine for additional control.
* Many unanswered questions remain about this medication that need to be studied to determine a more specific role in therapy. For example, what is the role of digoxin in comparison with ivabradine for heart rate control? Further studies are necessary to determine the full benefit of this agent.
* SACUBITRIL/VALSARTAN
* ARNIs are a new class of medications that may have a growing role in HF treatment. Sacubitril/valsartan is a novel therapy approved in July 2015 to reduce the risk of cardiovascular death and hospitalization for patients with HF*r*EF (NYHA class II–III). Sacubitril/valsartan consists of the neprilysin inhibitor sacubitril and the ARB valsartan. Neprilysin is a neutral endopeptidase that metabolizes endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and substance P into their inactive metabolites. Inhibition of neprilysin increases the levels of these substances and decreases vasoconstriction, sodium retention, abnormal growth, and remodeling.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b5-ptj4207464) However, angiotensin II is also a substrate of neprilysin. Thus, the addition of an ARB to the neprilysin inhibitor is necessary to prevent activation of the RAAS.
* Previous studies, such as OVERTURE, investigated the combination of a neprilysin inhibitor with an ACE inhibitor. Although the combination was shown to reduce mortality and hospitalization in chronic HF, it was not more effective than ACE inhibition alone and was associated with a higher rate of angioedema. Alternatively, PARADIGM-HF investigated the combination of the neprilysin inhibitor sacubitril and the ARB valsartan. PARADIGM-HF aimed to study the long-term effects of sacubitril/valsartan 200 mg twice daily on mortality and hospitalization compared with enalapril 10 mg twice daily in patients with HF*r*EF. To be considered for trial inclusion, patients were required to tolerate a stable dose of a beta blocker and an ACE inhibitor or ARB equivalent of at least 10 mg of enalapril daily for at least four weeks prior to trial screening. At baseline, of the 4,187 patients in the sacubitril/valsartan group, 78% were using an ACE inhibitor, 22.2% were on ARBs, 93.1% utilized a beta blocker, and 54.2% were taking an MRA. The study was stopped early (after the third interim analysis) due to a clear statistical and clinical advantage for sacubitril/valsartan; median follow-up was 27 months. The HR for sacubitril/valsartan for composite death from cardiovascular causes or first hospitalization for worsening HF was 0.80 (95% CI, 0.73–0.87; *P* < 0.001). Furthermore, when comparing sacubitril/valsartan with enalapril, the absolute risk reductions for death from cardiovascular cause and first hospitalization for worsening HF were found to be 3.2% (*P* < 0.001) and 2.8% (*P* < 0.001), respectively.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b5-ptj4207464) The total daily strength of the combination product used in the trial offered bioavailability similar to 320 mg valsartan. Although this is the desired target dose of valsartan according to the ACCF/AHA heart failure guidelines, the comparator (enalapril) was not pushed to its desired target dose. While less than the desired target dose, the studied dose of enalapril in PARADIGM-HF is reflective of the doses used in previous trials, such as CONSENSUS and SOLVD.Therefore, this new ARB and neprilysin inhibitor combination offers an additional option for patients who have optimized current guideline-supported therapies.
* Special consideration should be given when determining the appropriate dose of sacubitril/valsartan. Clinical trials, such as PARADIGM-HF, studied Entresto 200 mg, which includes sacubitril 97 mg and valsartan 103 mg. Available preparations now include a range of sacubitril and valsartan strengths, including the dose studied in PARADIGM-HF, as well as doses that were not studied in the trial, including sacubitril 24 mg/valsartan 26 mg and sacubitril 49 mg/valsartan 51 mg. The valsartan component in the combination product is more bioavailable than valsartan in other marketed formulations. Valsartan strengths of 26 mg, 51 mg, and 103 mg in sacubitril/valsartan offer a similar bio-availability to valsartan 40 mg, 80 mg, and 160 mg, respectively, in other marketed formulations.
* During the single-blind run-in period with enalapril and sacubitril/valsartan in PARADIGM-HF, 12.0% of the patients withdrew because of an adverse event.Adverse reactions to ARNIs include hypotension, hyperkalemia, increased serum creatinine, angioedema, cough, and renal failure. Although there were fewer incidences of angioedema in clinical trials with ARNIs than with the combined ACE and neprilysin inhibition, PARADIGM-HF showed that the risk of angioedema was still a concern. Angioedema occurred in 19 patients in the sacubitril/valsartan group and 10 patients in the enalapril group (*P* = 0.13). However, only 5% of the patients enrolled were African-American. Because African-Americans have a relatively higher risk of angioedema with ACE inhibitors and ARBs, the optimal agent for this high-risk population remains unclear. Monitoring parameters for ARNIs include baseline and periodic serum potassium, renal function, and blood pressure. ARNIs should be used with caution in patients with aortic/mitral stenosis, renal artery stenosis, or renal/hepatic impairment. Medications that work on the RAAS system (including ARNIs) should be discontinued as soon as pregnancy is detected because these agents can cause injury or death to the developing fetus.
* CONCLUSION
* Beta blockers and ACE inhibitors have been proven to reduce morbidity and mortality in a wide range of HF*r*EF patients. These proven benefits warrant the use of these agents in all patients with HF. MRAs such as spironolactone and eplerenone have also been shown to reduce morbidity and mortality in addition to ACE inhibitors and beta blockers in patients with HF*r*EF, depending on the NYHA class and EF. Therapy should always be individualized, but one of these agents can be added to base therapy for additional benefits. Vasodilators show morbidity and mortality benefit in African-American patients in specific situations and can be added to therapy.
* To help reduce morbidity in patients, additional agents may be added for symptomatic relief. In patients with signs and symptoms of fluid overload, diuretics should be used to help mobilize and excrete the excess fluid. Specifically, loop diuretics are seen as the first-choice agents, but thiazides may be added to overcome loop resistance. Digoxin may be added for symptom relief and to decrease morbidity. Though it does not show mortality reduction, it has demonstrated utility in decreasing hospitalizations for worsening HF*r*EF.
* Ivabradine may be added to treatment in patients on beta blockers who have persistently elevated heart rates or who cannot tolerate beta blockers. The addition of ivabradine will further reduce morbidity, mortality, and hospitalizations in these patients, because increased rates of cardiovascular death, hospitalization for HF and myocardial infarction, and coronary revascularization have been reported in patients with heart rates greater than 70 bpm.[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b52-ptj4207464),[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b55-ptj4207464) Thus, ivabradine should be considered add-on therapy in select patients with persistently elevated heart rates despite beta-blocker therapy.[56](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481297/#b56-ptj4207464)
* ARB and neprilysin inhibitor combination products (such as sacubitril/valsartan) offer a new option for patients. These agents may have a role in patients who remain symptomatic despite reaching maximum doses of ACE inhibitors/ARBs and beta blockers.