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Targeted ACE inhibitors for the Treatment of Dilated Cardiomyopathy (DCM)

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Abstract:

Dilated cardiomyopathy, a subtype of cardiomyopathies characterized by ventricular dilation, particularly of the left or both ventricles, coupled with systolic impairment, represents a heterogeneous condition distinct from valvular heart disorders, congenital cardiac anomalies, hypertensive cardiomyopathy, and acyanotic heart diseases. This article explores the varied categories of angiotensin-converting enzyme (ACE) inhibitors and their precise molecular targets. As a relatively uncommon disease entity, dilated cardiomyopathy lacks a definitive pharmacological cure and is managed primarily through medical therapy or surgical interventions. Emerging therapeutic modalities, such as left ventricular assist device (LVAD) support, have been introduced, yet the majority of these treatments necessitate careful consideration due to their specific indications and potential implications. Keywords: dilated cardiomyopathy, drug targeting, ACE inhibitors

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1. Introduction

1.1 Symptoms

The symptoms of DCM are varied, including heart failure, arrhythmia, sudden death and so on. The early stage may be asymptomatic or mild, and the late stage will have obvious symptoms of heart failure. Patients may experience dyspnea, paroxysmal dyspnea at night, decreased activity tolerance, etc., and may also include decreased appetite, abdominal distention and lower limb edema. When patients with pulmonary embolism, there may be chest pain, coughing up blood and other symptoms. Department for treatment: Vasculocardiology Department

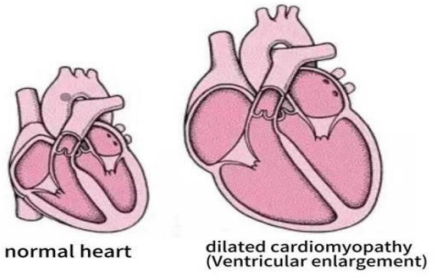

Fig.1 shows the comparison between normal heart and dilated cardiomyopathy heart

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1.2 Pathogenesis

Dilated cardiomyopathy (DCM), a subtype of cardiomyopathies, is marked by ventricular dilation, particularly involving the left or both ventricles, accompanied by systolic impairment. Its etiology encompasses a wide spectrum, ranging from infections and immune-mediated processes to genetic predispositions, toxic exposures, and metabolic disturbances. Notably, a significant proportion of DCM cases remain idiopathic, with their underlying causes yet to be elucidated.

The European Society of Cardiology (ESC) categorizes cardiomyopathies into familial (genetic) and non-familial (non-genetic) subsets, offering a framework for understanding their origins [1][2]. Furthermore, the World Health Organization (WHO) designates DCM as a critical cardiac condition, characterized by structural or functional alterations in myocardial tissue, which can significantly contribute to morbidity and mortality through complications such as heart failure and cardiac arrhythmias [3]. This classification underscores the gravity of DCM and the need for comprehensive management strategies.

1.2.1 Cause of dilated cardiomyopathy

1.Regarding Genetic Mutations: Approximately 20 to 30 percent of instances of dilated cardiomyopathy (DCM) are genetically linked. These often involve alterations in the genetic blueprints responsible for the creation of heart muscle filaments (myocardial myofibrils), which subsequently correlate with DCM occurrence.

2.Coronary Artery Disease (CAD) Influence: Coronary artery disease can inflict harm upon the cardiac musculature, ultimately culminating in diminished blood perfusion to the heart. This inadequate blood flow, in turn, fosters the emergence of DCM.

3.Chronic Hypertension Impact: Prolonged exposure to elevated blood pressure levels may provoke the thickening and stiffening of heart muscle tissue, a process that may eventually precipitate DCM.

4.Contributions of Toxic and Metabolic Imbalances: Factors such as excessive alcohol intake, exposure to harmful substances like chemotherapeutic agents, disruptions in thyroid function, and imbalances in electrolyte levels all play a role in precipitating the development of DCM.

5.Infectious Etiologies of DCM: A diverse array of pathogens have been implicated as causative agents of DCM, highlighting the complexity of this cardiac condition.

Viruses encompass a diverse array, including adenovirus species, coronavirus species, coxsackievirus (both groups A and B), cytomegalovirus species, dengue virus, echovirus species, Epstein-Barr virus, hepatitis B and C viruses, herpes simplex virus, human herpesvirus 6, HIV, influenza A and B viruses, rubulavirus causing mumps, parvovirus B19, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, measles virus, and Varicella-zoster virus. Among bacteria, we find β-haemolytic streptococci, Borrelia burgdorferi, Brucella species,

Campylobacter jejuni, Chlamydia species, Clostridium species, Corynebacterium diphtheriae, Neisseria species, Haemophilus influenzae, Legionella pneumophila, Listeria monocytogenes, Mycoplasma pneumoniae, Neisseria meningitidis, Salmonella serotypes (Berta and Typhi), Streptococcus pneumoniae, Staphylococcus species, and Treponema pallidum. Protozoa are represented by Entamoeba histolytica, Leishmania species, Plasmodium vivax, Plasmodium falciparum, Toxoplasma gondii, and Trypanosoma cruzi. Helminths encompass Taenia species, Echinococcus species, Schistosoma species, Toxocara species, and Trichinella species. Fungi, meanwhile, consist of Actinomyces species, Aspergillus species, Candida species, Coccidioides immitis, and Cryptococcus neoformans.[4]

7.Autoimmune diseases: Some autoimmune diseases, such as lupus or rheumatoid arthritis, can affect the heart muscle and cause DCM.

8.Pregnancy: DCM can occur during or after pregnancy, and this condition is called childbirth cardiomyopathy, although the exact cause is not fully understood.

9.Idiopathic: In many cases, the cause of DCM is unknown, so these are called idiopathic DCM. 10.Age and gender: DCM is more common in men than women and usually occurs in middle-aged and older people.

1.3 Morbidity&Mortality rate in China and in the whole world

1.3.1 Current Morbidity in China

The current incidence data in China is 13/100 000 ~ 84/100 000. The morbidity of males and females is 2.5:1.

1.3.2 Current Mortality Rate in Africa

DCM has a high all-cause mortality rate.

Mid-wall late gadolinium enhancement was visualized in 61% of participants.[5]

1.3.3 Current mortality rate in the whole world

The timing of diagnosis significantly impacts mortality rates, with earlier identification resulting in decreased mortality. Additionally, for certain heart conditions, patients can experience complete normalization post-treatment. For instance, alcoholic cardiomyopathy can achieve a state of full recovery if the cessation of alcohol consumption is prompt and accompanied by rigorous therapeutic intervention. Conversely, when dilated cardiomyopathy progresses to heart failure, the prognosis diminishes; studies indicate a 5-year mortality rate of 35%, escalating

to over 70% within 10 years. Notably, upon reaching heart failure, three-quarters of patients experience accelerated deterioration, with half or even two-thirds succumbing within two years, equating to a 2-year mortality rate of approximately 65%. Hence, prompt and accurate diagnosis, followed by timely treatment, is paramount in enhancing overall outcomes and prognosis for these conditions.

1.3.4 Comparison of mortality risk between different races

Multiple investigations have documented a comparative risk of death due to dilated cardiomyopathy (DCM) ranging from 1.2 to 1.5 in African American individuals when juxtaposed with their age-equivalent Caucasian counterparts. Notably, this observation cannot be solely attributed to variations in hypertension levels or socioeconomic determinants, as previously outlined in references.[6][7]

2. Materials and methods

2.1 Drugs used to treat the disease and their origins

Angiotensin-Converting Enzyme (ACE) inhibitors (USA, Europe), Angiotensin Receptor Blockers(ARBs)(USA), Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) (Swiss), Beta blockers (UK), mineralocorticoids receptor antagonists (MRAs), Sodium-glucose cotransporter 2(SGLT2) (Japan).

2.2 Purposes of heart medication

Help DCM patients live longer, improve heart muscle, and reduce stress on the heart.

2.3 More detailed description of drugs

ACE inhibitors/ARBs/ARNIs: These medications facilitate the enhancement of cardiac muscular strength in patients and contribute to the expansion or dilation of blood vessels. Consequently, they augment the volume of blood circulated by the heart, resulting in a reduction in blood pressure. Furthermore, they enhance blood circulation, thereby alleviating the workload imposed on the heart, which is a crucial factor in improving cardiac function.
ACE inhibitors: ACE inhibitors operate by inhibiting the catalytic function of angiotensin-converting enzyme, an enzyme pivotal in the conversion of angiotensin I into angiotensin II. Angiotensin II, being a potent vasoconstrictive agent, has the capability to induce vasoconstriction, ultimately elevating blood pressure. The suppression of ACE by these medications curtails the production of angiotensin II, thereby prompting vasodilation and a consequential reduction in blood pressure levels.
For clinical purposes, ACE inhibitors work to treat hypertension and heart failure, it can also prevent further damage to the heart muscle after a heart attack.
ARBs: Angiotensin II, a powerful vasoconstrictor, typically causes blood vessels to constrict, raising blood pressure. By blocking its receptors, ARBs counteract this constriction, promoting vasodilation and reducing blood pressure levels.
ARNIs: The utilization of a combination therapeutic approach, incorporating an angiotensin receptor blocker (ARB) and Sacubitril, which inhibits the degradation of a vital hormone instrumental in mitigating the symptoms and sequelae of congestive heart failure, has garnered attention.
Beta blockers: more formally referred to as beta-adrenergic blocking agents, represent a class of medications that act to suppress the activity of specific endogenous chemical messengers within the body. Their mechanism of action revolves around blocking the adverse effects of sustained elevated levels of epinephrine (adrenaline), a hormone that can be detrimental to cardiac function in individuals with dilated cardiomyopathy (DCM) and reduced ejection fraction. This blockade results in slowed and weakened cardiac contractility, ultimately leading to reduced blood pressure and diminished workload on the heart, adhering to the principles of evidence-based medicine.
MRAs: a kind of medicine which shows improvement in survival and sudden cardiac death in DCM patients who have a reduced ejection fraction. MRAs inhibit the action of aldosterone, which is a hormone that regulates sodium and potassium balance in the body, by blocking the mineralocorticoid receptor (MR).
SGLT2 inhibitors: provide benefits to patients with DCM and reduced ejection fraction of 40% or more. They reduce the risk of hospitalization for heart failure and cardiovascular death.

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2.4 Chemical structures of drugs

2.4.1 Chemical structure of ACE inhibitors

Fig.2 shows the chemical structures of ACE inhibitors

2.4.2 descriptions of the ACE inhibitors

2.4.2 .1 Enalapril Maleate

Description: Enalapril maleate constitutes the maleate salt derivative of enalapril, involving an equimolar ratio of maleic acid to enalapril. Upon oral ingestion, the ethyl ester moiety of enalapril undergoes hydrolysis, yielding enalaprilat, a potent angiotensin-converting enzyme (ACE) inhibitor. Essentially, enalapril serves as a prodrug precursor to enalaprilat, which is not directly absorbed via the oral route. The maleate formulation of enalapril is therapeutically employed for the management of hypertension and cardiac insufficiency, mitigating proteinuria and renal complications in nephropathic patients, as well as prophylactic measures against stroke, myocardial infarction, and cardiac mortality in individuals considered at high risk.

Chemical and Physical properties

Its molecular formula is $C_{24}H_{12}N_2O_{5,}$ molecular weight is 492.5g/mol , hydrogen bond donor count is 4 and hydrogen bond acceptor count is10. Chemical Entities of Biological Interest (ChEBI)

The enalapril maleate form, a dicarboxylic acid-containing peptide and ACE inhibitor, exhibits antihypertensive capabilities. It functions as a prodrug, transforming into its bioactive counterpart through de-esterification. Subsequently, enalaprilat competitively binds to ACE, impeding its activity and blocking the conversion of angiotensin I to angiotensin II. This action also precludes the potent vasoconstrictive effects of angiotensin II, thereby promoting vasodilation. Furthermore, enalapril diminishes aldosterone secretion instigated by adrenocortical angiotensin II, ultimately leading to increased sodium excretion and, subsequently, heightened water excretion.

Pharmacology & Biochemistry

ACE inhibitors

A group of medications primarily prescribed for the control of hypertension and heart failure predominantly induces hemodynamic alterations via suppression of the renin-angiotensin system. Additionally, these therapeutic agents modulate the functioning of the sympathetic nervous system and provoke an increase in prostaglandin synthesis. Their core effects encompass vasodilation and a modest enhancement of sodium excretion while exhibiting negligible impact on heart rate or contractility.

Antihypertensive Agents

A multitude of medications utilized in the therapeutic strategy for both acute and chronic presentations of vascular hypertension, regardless of their distinct pharmacological mechanisms, encompass a diverse array of classes. These agents aimed at reducing hypertension encompass diuretics (specifically, thiazide-type diuretics), beta-adrenergic antagonists, alpha-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, modulators of calcium channels, inhibitors of ganglionic neurotransmission, vasoactive agents that elicit vasodilation.

Chemical-Target Interactions

Its protein is the Angiotensin-converting enzyme; the gene is ACE, which mainly has effects on Homo sapiens (humans). Its action is an ACE inhibitor.

2.4.2 .2 Lisinopril dihydrate

Description: Lisinopril dihydrate is a hydrate. It has a role as an antihypertensive agent. It contains lisinopril.

Chemical and Physical properties

Its molecular formula is $C_{21}H_{35}N_3O_7$, molecular weight is 441.5g/mol, hydrogen bond donor count is 6 and hydrogen bond acceptor count is 9. Chemical Entities of Biological Interest (ChEBI)

Lisinopril, a synthetic peptide analogue, represents an orally administered, prolonged-action ACE inhibitor renowned for its potent antihypertensive capabilities. It functions by competitively and selectively inhibiting ACE, resulting in a reduction in the production of angiotensin II, a potent vasoconstrictive hormone, thereby mitigating its vasopressor effects. Additionally, lisinopril

attenuates angiotensin II-induced aldosterone secretion from the adrenocortical glands, contributing to decreased sodium and water retention, as well as an augmentation in serum potassium concentrations.

Pharmacology & Biochemistry ACE inhibitors

A group of therapeutic agents, predominantly utilized in the management of hypertension and cardiac insufficiency, exerts their remedial effects by inhibiting the renin-angiotensin cascade, subsequently modulating various hemodynamic indices. Furthermore, they modulate the activity of the sympathetic nervous system and augment prostaglandin biosynthesis. Notably, these agents primarily elicit vasodilation and induce a mild natriuretic response without significantly influencing cardiac rate or contractility.

Antihypertensive Agents

An extensive spectrum of medications, diverse in their pharmacological profiles, is utilized for the management of both acute and chronic forms of vascular hypertension. This comprehensive category incorporates diuretics, notably thiazide diuretics, in addition to adrenergic beta-adrenoreceptor antagonists, adrenergic alpha-adrenoreceptor antagonists, ACE inhibitors, voltage-gated calcium channel blockers, ganglionic neurotransmission blockers, and vasoactive agents that promote vasodilation.

Cardiotonic Agents

A medication designed to fortify cardiac function or augment cardiac output encompasses cardiac glycosides, sympathomimetic agents, and various other therapeutic entities. These drugs find application subsequent to myocardial infarction, cardiac surgical procedures, shock states, or in the management of congestive heart failure.

Chemical-Target Interactions

Its protein is Angiotensin-converting enzyme, gene is ACE, have effects on Homo sapiens (human). Its action is ACE inhibitor.

2.4.2 .3 Captopril

Description: Captopril, a derivative of L-proline, involves the substitution of L-proline's nitrogen atom with (2S)-2methyl-3-thioalkylpropionyl. This compound serves as an angiotensin-converting enzyme (ACE) inhibitor for antihypertensive purposes. Its mechanism of action includes inhibiting EC3.4.15.1 (peptidyl-dipeptidase A), contributing to its antihypertensive effects. Structurally, it is a pyrrolidine monocarboxylic acid derivative, belonging to the classes of N-acyl pyrrolidines, and alkyl mercaptans and being a modification of Lproline.

Chemical and Physical properties

Its molecular formula is $C_9H_{15}NO_3S$, molecular weight is 217.29g/mol, hydrogen bond donor count is 2 and hydrogen bond acceptor count is 4. Chemical Entities of Biological Interest (ChEBI)

Captopril acts as a potent and competitive antagonist of ACE inhibitors, the enzyme pivotal in converting angiotensin I (ATI) to angiotensin II (ATII), a vital regulator of blood pressure and a core element within the renin-angiotensin-aldosterone system (RAAS). This medication is employed in the management of hypertension.

Pharmacology& Biochemistry ACE inhibitors

Captopril, a form of ACE inhibitor, disrupts the renin-angiotensin-aldosterone system (RAAS), a homeostatic mechanism governing hemodynamic regulation, water, and electrolyte equilibrium. Upon stimulation of sympathetic nerves, diminished renal perfusion, or blood flow, renin is liberated from granular kidney cells. Circulating angiotensinogen is then cleaved by renin into angiotensin I (ATI), which subsequently undergoes further cleavage to angiotensin II (ATII). ATII exerts multiple mechanisms to elevate blood pressure. Firstly, it triggers aldosterone secretion by the adrenal cortex, augmenting sodium and water reabsorption in the distal convoluted tubules (DCT) and collecting ducts of nephrons via up-regulation of sodium channels and sodium-potassium ATPase on cell membranes. Secondly, ATII prompts the posterior pituitary gland to secrete vasopressin (ADH), further enhancing renal water retention through aquaporin-2 channel insertion into DCT and collecting tubule apical membranes. Thirdly, ATII directly elevates blood pressure by inducing arterial vasoconstriction, mediated by Type 1 ATII receptor stimulation on vascular smooth muscle cells, resulting in a cascade leading to muscle contraction and vessel narrowing. Additionally, ATII elicits thirst by stimulating hypothalamic neurons. By inhibiting the rapid transformation of ATI to ATII, ACE inhibitors counteract the hypertensive effects of RAAS. Furthermore, ACE's involvement in bradykinin's enzymatic inactivation is hindered, enhancing bradykinin levels, which may perpetuate vasodilation and hypotension.

A class of medications utilized for hypertension and cardiac insufficiency management primarily modulates hemodynamics by inhibiting the renin-angiotensin system. They also regulate sympathetic activity and enhance prostaglandin synthesis, primarily inducing vasodilation and mild natriuresis without affecting heart rate or contractility. Antihypertensive Agents

A multitude of therapeutic agents, regardless of their distinct pharmacological mechanisms, are used in managing both acute and chronic vascular hypertension. These encompass diuretics, especially thiazides, adrenergic beta- and alpha-blockers, ACE inhibitors, calcium channel blockers, ganglionic blockers, and vasoactive agents that promote vasodilation.

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2.5 Preparation of ACE Inhibitors

2.5.1 Synthesis of ACE Inhibitors

2.5.1 .1 Synthesis of Enalapril Maleate

To conduct the synthesis, initially, benzoyl alcohol, L-alanine, toxic acid, and a suitable solvent are introduced into the reaction vessel. Subsequently, the mixture is gradually heated to initiate reflux, allowing the reaction to proceed to completion. Following this, vacuum distillation is employed to purify the product, which is then cooled to ambient temperature. At this point, ethyl acetate is introduced, and the solution is further cooled to 0°C to induce crystallization. The resultant crystals are then filtered, washed thoroughly, and dried to yield compound 2. Subsequently, compound 2 is dissolved in an appropriate solvent, and ethyl 1-benzoylpropionate is added. The mixture is vigorously stirred, and triethylamine is incrementally introduced at 40°C. The reaction mixture is maintained at this temperature for 1 hour under stirring, followed by gradual cooling to 0°C to facilitate crystallization. The product is then extracted, filtered, washed, and dried to obtain white acicular crystals of compound 3. For the subsequent step, compound 3 is combined with vitriol oil, acetic acid, and 10% Pd/C in an autoclave under a pressure of 0.8MPa. The reaction is carried out at room temperature, followed by cooling and filtration. The filtrate is treated with sodium acetate, and neutralization is performed over 1 hour. Acetic acid is then distilled off until the solution becomes viscous, and water is added. After stirring for 30 minutes, the mixture is extracted, and the organic layer is separated, washed with saturated saline solution, and the solvent is removed by evaporation. Recrystallization in 50% ethanol yields compound 4. Compound 4 is dissolved in THF, and di(trichloromethyl) carbonic acid is added to the tetrahydrofuran solution under continuous agitation. The mixture is stirred at room temperature for 1 hour and then heated to 50°C to initiate the reaction. Following completion, THF is removed by vacuum distillation, and acetone is added to the residue for further use. [8]

2.5.1 .2 Synthesis of Lisinopril

As the second most frequently prescribed generic medication, lisinopril belongs to the angiotensin-converting enzyme (ACE) inhibitor class and serves as a primary therapeutic option for the management of hypertension. It stands as the third ACE inhibitor in succession, following captopril and enalapril, and its chemical nomenclature is N2-[(1S)-1-Carboxy3phenylpropyl]-L-lysyl-L-proline.

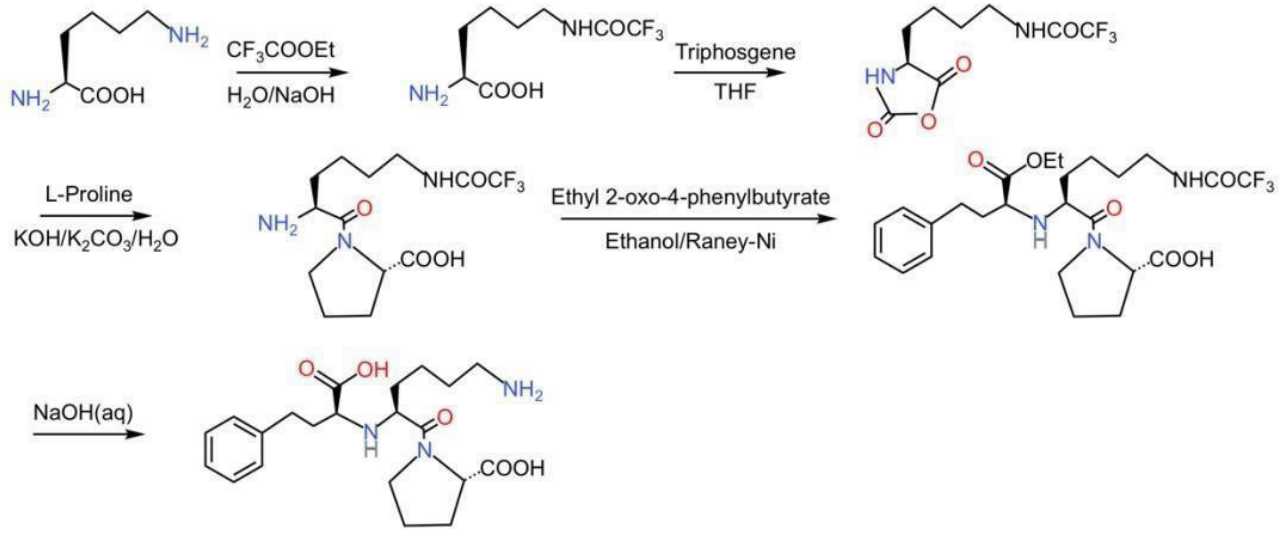

Fig.3 shows the synthesis of Lisinopril

2.5.1 .3 Synthesis of Captopril

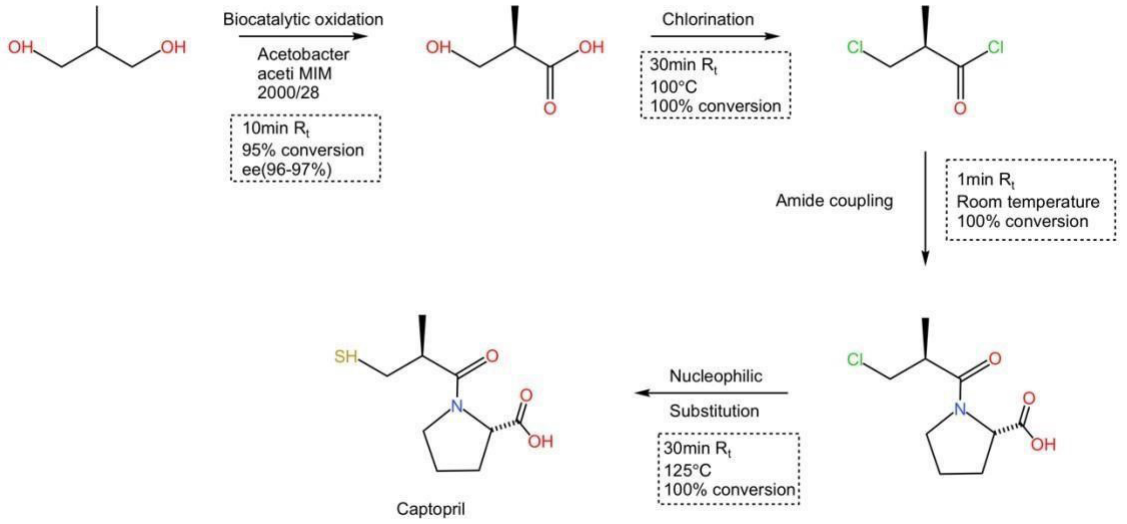

Fig.4 shows the synthesis of Captopril

2.5.2 Guidelines for taking ACE inhibitors

Administer ACE inhibitors on an empty stomach, ideally an hour prior to meals, adhering strictly to the package instructions regarding dosage frequency. The daily dosage regimen, including dosage intervals and treatment duration, varies according to the specific ACE inhibitor prescribed and individual patient conditions. While undergoing ACE inhibitor therapy, refrain from using salt substitutes, as they contain potassium, which this medication can elevate in the body. Instead, opt for meals low in both sodium and potassium. Moreover, avoid self-medicating with over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs, such as Aleve or Motrin), as they may promote sodium and water retention, thereby diminishing the efficacy of ACE inhibitors. Regular monitoring of blood pressure and renal function is crucial. Abrupt cessation of ACE inhibitor therapy, even if perceived as ineffective, should never occur without prior medical consultation. In cases of heart failure treatment, patients should understand that symptomatic improvement may not be immediate. Nevertheless, consistent, long-term use of ACE inhibitors is instrumental in managing chronic heart failure effectively. [9]

2.6 Mechanisms of ACE inhibitors

2.6.1 Mechanism of Enalapril Maleate

Enalapril, a potent ACE inhibitor, operates by hindering a physiological factor that initiates vasoconstriction, thereby inducing vasodilation. This action promotes the relaxation of blood vessels, decreasing blood pressure and augmenting cardiac perfusion, enhancing blood and oxygen supply to the heart. Moreover, it can be integrated into therapeutic regimens alongside other medications for managing congestive heart failure.

2.6.2 Mechanism of Lisinopril

Lisinopril, an ACE inhibitor, disrupts the conversion of angiotensin I to II. The renin-angiotensin system, naturally, elevates blood pressure via pressure receptor augmentation and vasoconstrictor secretion, especially during stress or ischemia. Lisinopril administration halts ACE activity, lowering angiotensin II, promoting vascular and muscular relaxation, vasodilation, and, ultimately, blood pressure reduction. It also alleviates peripheral vascular resistance, often augmented by angiotensin-mediated water-sodium retention, thereby maintaining normal blood pressure. Moreover, lisinopril exhibits immunomodulatory effects, enhancing macrophage phagocytosis and antimicrobial peptide expression, suggesting therapeutic benefits in hypertension complicated by bacterial infections.

2.6.3 Mechanism of Captopril

Captopril exerts dual antihypertensive mechanisms. Firstly, it inhibits angiotensin II's production and subsequent vasoconstrictive effects, thereby dampening aldosterone secretion from the adrenal cortex. This alleviates aldosterone-mediated water-sodium retention, facilitating blood pressure reduction. Secondly, Captopril impedes bradykinin degradation, boosting its circulation. This augmentation triggers the production of vasodilators, including prostaglandins and nitric oxide, which expand blood vessels, further aiding in blood pressure reduction.

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2.7 Targeted ACE Inhibitors for DCM

2.7.1 Cells that ACE inhibitors act on

Endothelial cells: ACE inhibitors enhance the action of bradykinin, a vasodilating factor produced by endothelial cells. The bradykinin acts on vascular smooth muscle through its receptors, causing blood vessels to dilate. ACE inhibitors can reduce endothelial cell production of endothelin and help vascular dilation.

Vascular smooth muscle cells: By reducing the production of angiotensin II, ACE inhibitors reduce the contraction of vascular smooth muscle, thereby leading to vasodilation and decreasing in blood pressure. Angiotensin II promotes the proliferation and migration of vascular smooth muscle cells, and ACE inhibitors inhibit these effects by reducing the production of angiotensin II, which helps prevent vascular reconstruction.

Cardiomyocytes: ACE inhibitors reduce the risk of cardiac hypertrophy by decreasing the production of angiotensin II, as the angiotensin II may stimulate the growth of cardiomyocytes.

At the case of heart failure, ACE inhibitors can improve the structure and function of heart, it reduces myocardial fibrosis and helps to maintain normal heart function.

Sympathetic nerve endings: ACE inhibitors can reduce the release of norepinephrine from sympathetic nerve endings, which is a strong cardiovascular stimulant, and its reduction helps to decrease the burden on the cardiovascular system. fibroblast: At the case of heart failure, ACE inhibitors can reduce the activation of fibroblasts and the deposition of collagen, thereby decreasing myocardial fibrosis.

2.7.2 How ACE inhibitors act on DCM treatment

Decreasing angiotensin II generation leads to blood pressure reduction. Angiotensin II fosters cardiac hypertrophy and remodeling; however, ACE inhibitors hinder its formation, assisting in preventing or reversing these detrimental processes and ultimately safeguarding cardiac function. By curbing angiotensin II synthesis, ACE inhibitors mitigate fibrosis within the heart, as angiotensin II stimulates this fibrotic response. Furthermore, ACE inhibitors modulate the excessive activity of the RAAS and sympathetic nervous system, which may contribute to dilated cardiomyopathy (DCM) development. Lastly, by reducing angiotensin II production, ACE inhibitors diminish aldosterone stimulation.

2.8 Side effects of ACE inhibitors

Dry cough, high potassium levels in the blood, and low blood pressure lead to extreme fatigue or dizziness, headaches, loss of waste, and (in rare cases) kidney function deteriorates in the short term. [10]

2.9 New medication for DCM

2.9.1 Diuretics

Function: They treat high blood pressure and heart failure by helping patients' kidneys produce more urine. The more patients urinate, the more salt and water they expel from their bodies. Without excess fluid, the heart can pump blood more easily.

Examples: Furosemide, Spironolactone

Benefits: Reduce congestion and shortness of breath.

Side effects: The manifestation of frequent urination, coupled with sensations of lightheadedness and profound fatigue, often accompanies alterations in bowel movements and the occurrence of muscular cramps. In some instances, males may infrequently encounter difficulties with erectile function, a phenomenon noted in the literature.[11]

2.9.2 Aldosterone Antagonists

Function: Aldosterone receptor antagonists hinder the actions of aldosterone, thereby inhibiting the reuptake of sodium, a process that fosters water excretion. Consequently, this mechanism contributes to a reduction in blood pressure levels and alleviates fluid accumulation surrounding the heart. These antagonists find application in managing hypertension and cardiac insufficiency.[12] Furthermore, they are efficacious in treating hyperaldosteronism, edema (fluid accumulation) stemming from hepatic or renal ailments, chronic kidney disease, hypokalemia (low potassium concentration), left ventricular dysfunction (impairment of the heart's primary pumping chamber), post-myocardial infarction heart failure or diabetes, as well as acne, a condition often prescribed for by dermatologists.

Examples: Spironolactone, eplerenone [13]

Benefits: To prolong survival rates, minimize hospital admissions, and enhance the symptomatic outcomes in individuals diagnosed with moderate to severe chronic systolic heart failure, along with those experiencing heart failure in the immediate aftermath of a myocardial infarction.[14]

Side effects: High potassium levels, kidney problems, male changes (this may occur when taking spironolactone)

3. Treatment of DCM

3.1 Diagnosis of DCM

Physical Evaluation: A meticulous cardiac auscultation detected prominent third and fourth heart sounds, accom-

panied by diminished cardiac tones and evident cardiac enlargement. Pulmonary auscultation unveiled moist rales at lung bases, while a comprehensive assessment might also uncover peripheral edema, jugular venous dissension, and ascites, indicative of dilated cardiomyopathy.

Imaging Techniques: If the physical examination correlates with dilated cardiomyopathy's clinical picture, chest Xray will show an enlarged cardiac silhouette with signs of pulmonary congestion, pleural effusion, and other relevant indicators. Cardiac MRI clarifies myocardial fibrosis, while echocardiography depicts cardiac enlargement and a spherical shape, typically confirming the diagnosis.

Specialized Investigations: For select patients, further evaluations like ECG and endocardial myocardial biopsy may be necessary. ECG findings, like abnormal P-wave patterns, distorted QRS complexes, and ST-T changes, combined with biopsy results showing nuclear abnormalities, cytoplasmic vacuoles, and cardiomyolysis instances, augment dilated cardiomyopathy diagnosis. [15]

3.2 Therapy of DCM

3.2.1 Drug therapy

Revised Therapeutic Approach for Dilated Cardiomyopathy (DCM): Addressing the fundamental etiology of DCM necessitates tailored immunological therapy, particularly for immune-mediated cases. Expedient medical intervention to mitigate ventricular remodeling is imperative, with beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ARBs) forming the therapeutic backbone. The paramount objective is to minimize myocardial damage, halt disease progression, and enhance the prognosis for adults with heart failure and DCM.

Intermediate Therapeutic Tactics: Confronting the pathophysiological mechanisms underlying heart failure involves targeting dysregulated activations in the sympathetic nervous system, renin-angiotensin-aldosterone axis, and natriuretic peptide system. Essential therapeutic modalities encompass beta-blockers, ACE inhibitors, ARBs, angiotensin receptor-neprilysin inhibitors (ARNIs), and aldosterone antagonists. The primary focus is on reducing morbidity and mortality in heart failure patients. Additionally, prudent diuretic usage and sodium restriction, primarily with agents like hydrochlorothiazide and furosemide, aim to manage fluid retention, alleviate cardiac stress, and optimize patient outcomes.

Advanced Therapeutic Interventions: When conventional pharmacotherapy fails to alleviate heart failure symptoms, consideration may be given to administering intravenous positive inotropic agents, like dobutamine. Furthermore, vasodilators such as nitroglycerin and sodium nitroprusside can augment therapy, striving to further enhance cardiac function and alleviate the burden of heart failure.

3.2.2 Surgical treatment Heart transplantation

Indications: the peak oxygen consumption of the cardio exercise test was<14ml/ (kg-min) in patients who could not tolerate beta-blockers, and <12ml /(kg-min) in patients who were using betablockers; Patients>70 years old may be considered for heart transplantation after careful evaluation; Patients with Body Mass Index (BMI)>35kg/m^2 have a worse prognosis after heart transplantation, so it is recommended that BMI of such obese patients be reduced to ≤35kg/m^2 before surgery.

3.2.3 Other treatments

Cardiac Resynchronization Therapy (CRT), a precise treatment for heart failure, is prescribed for individuals with sinus rhythm exhibiting a prolonged QRS duration over 150 milliseconds, concurrent with left bundle branch block. CRT is indicated in refractory cases, where medical management fails to alleviate persistent symptoms and left ventricular ejection fraction (LVEF) declines below 35%. Its primary objective is to restore synchronous ventricular contraction, thereby alleviating mitral regurgitation in heart failure patients with significant left-right ventricular dyssynchrony. This therapeutic approach enhances cardiac output and optimizes cardiac function. Auxiliary devices encompass supportive technologies like intra-aortic balloon pump counter-pulsation, extracorporeal membrane oxygenation for oxygenation, and ventricular assist devices, which are vital in managing advanced dilated cardiomyopathy, especially during hemodynamic instability, cardiogenic shock, and critical conditions.

Immunological therapy addresses the autoimmune mechanisms underlying dilated cardiomyopathy (DCM), particularly targeting anti-myocardial antibodies. Beta-blockers are the preferred treatment for patients with beta1adrenergic receptor (beta1AR) antibodies, while Diltiazem may benefit those with anti-L-type calcium channel (anti-L-CAC) antibodies. Immunosorbent therapy effectively improves cardiac function in DCM patients with autoantibody-mediated myocarditis (AHA) positivity. Additionally, immunomodulatory therapy aims to prevent myocardial damage by preemptively addressing abnormal immune responses in early-stage DCM.

3.3 Prognosis

Where the etiology is removed is very important to the prognosis of the disease. Data from previous studies show that after diagnosis of the disease, the 5-year survival rate is about 50%, and the 10-year survival rate is about 25%.

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In recent years, with the progress of treatment methods, patients with active cooperation and regular treatment have significantly improved prognoses.

3.4 Recovery policy

More rest.
Reduce the work of heart, pay attention to bed rest. Proper limb movements can be carried out in bed to prevent the formation of blood clots.
Limit sodium and water intake.
Reduce cardiac preload. Sodium intake<3g/day, liquid intake 1.5-2L/day. Control and remove external factors that may aggravate heart failure.
Control weight to avoid obesity or cachexia. Control infection, hypertension, diabetes, anaemia, etc.
Proper movement.
Carry out appropriate aerobic exercise under the monitoring of medical staffs, increasing exercise tolerance and improving quality of life is the core content of cardiac rehabilitation treatment.
Improve sleep.
Regular work and rest schedules ensure adequate sleep and avoid neurological disorders.
Strengthen psychological counseling Pay attention to reduce mental stress.

4. Conclusion

The goal of this study is to discuss the clinical features and treatment of dilated cardiomyopathy. By studying the cases and the literature, I came to a conclusion. The clinical manifestations of dilated cardiomyopathy are varied, but the most typical features include enlargement of the heart, decreased ventricular systolic function, and possible symptoms of congestive heart failure. Patients may have no obvious symptoms in the early stage and may develop extreme fatigue, weakness, shortness of breath and other symptoms as the disease progresses. Ventricular or atrial arrhythmias are common, and the condition is usually progressive. Current drugs include ACE inhibitors, beta-blockers, etc., which can effectively control symptoms, improve heart function, and delay the progression of the disease. Through drug treatment, the patient's symptoms are relieved, the heart function is restored, and the quality of life is significantly improved. Although there are many treatment methods, the etiology and pathogenesis of dilated cardiomyopathy are still not in-depth, and further basic research is needed. New therapeutic strategies and technologies need to be explored, such as the application of cutting-edge technologies such as gene therapy and stem cell therapy in the treatment of dilated cardiomyopathy.

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