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Mechanism and use strategy of uric acid-lowering drugs on coronary heart disease

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ABSTRACT

Coronary heart disease (CHD) is a serious cardiovascular illness, for which an elevated uric acid (UA) level presents as a considerable risk factor. This can be treated with UA-lowering drugs such as allopurinol and benzbromarone, which can reduce UA levels by the inhibition of UA production or by promoting its excretion. Such drugs can also be beneficial to CHD in other ways, such as reducing the degree of coronary arteriosclerosis, improving myocardial blood supply and alleviating ventricular remodeling. Different UA-lowering drugs are used in different ways: allopurinol is preferred as a single agent in clinical application, but in absence of the desired response, a combination of drugs such as benzbromarone with ACE inhibitors may be used. Patients must be monitored regularly to adjust the medication regimen. Appropriate use of UA-lowering drugs has great significance for the prevention and treatment of CHD. However, the specific mechanisms of the drugs and individualized drug use need further research. This review article expounds the mechanisms of UA-lowering drugs on CHD and their clinical application strategy, thereby providing a reference for further optimization of treatment.

1. Introduction

Coronary heart disease (CHD) is a serious cardiovascular illness, often with fatal outcome [1]. The World Health Organization (WHO) recorded 19,333 cardiovascular events over a 10-year follow-up period, including 18,987 fatal or non-fatal myocardial infarction or CHD deaths [2]. The morbidity and mortality of CHD vary among regions and populations [3]. Classical risk factors for CHD account for the majority of the global risk of myocardial infarction [4]. In data from 79 countries, the risk of developing CHD at 10 years greater than 20 % in people aged 40–64 years ranges from less than 1 % to more than 16 % according to WHO model estimates [2].

Many factors contribute to cardiovascular disease, including elevated UA blood levels [5]. UA is a metabolite of purine nucleotide degradation and is excreted via urine. Patients with hyperuricemia have a 9 % increase in the morbidity of CHD and a 13 % increase in CHD mortality compared with a normal population, and lowering UA levels can be protective [6]. UA levels closely correlated to the occurrence and progression of CHD. High levels of UA can lead to abnormal endothelial cell function, impaired vasoconstriction, and increased blood viscosity, all of which increases the risk of CHD [7,8]. Therefore, lowering UA levels may be an effective strategy for the prevention and treatment of CHD.

Control through medication and lifestyle changes are the main means of lowering UA levels [9]. The mechanism of action of UA-lowering drugs is mainly divided into two categories: inhibiting UA production and promoting UA excretion [10]. UA production can be inhibited by xanthine oxidase inhibitors (XOIs) such as allopurinol, which inhibit the step of xanthine oxidation leading to UA production and can also improve vascular endothelial function [11–13]. An example of a UA excretion drug is lesinurad, which promotes UA excretion by selectively inhibiting renal UA transporter 1 (URAT1) [14].

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By lowering UA levels in the blood, these drugs reduce the interaction of UA with vascular endothelial cells, thereby improving vascular function. Reduced UA levels also reduce systemic inflammation and the production of oxidative substances, contributing to a reduced risk of CHD [6].

Although the mechanistic actions of these drugs towards their substrate targets is well known, the specific mechanism of action of UA-lowering drugs for reducing CHD risk is not fully understood, and their clinical use is far from perfect. In order to ensure the best balance between efficacy and safety, an individualized treatment plan should ideally be developed according to the specific situation of the patient. For more general improvements, further research needs to be carried out in depth. This article reviews the our mechanistic understanding of the effect of UA-lowering drugs on CHD and describes its use strategies, in order to provide clinicians with more effective means for the prevention and treatment of CHD.

2. Mechanism of action of UA-lowering drugs

2.1. Reducing UA production by enzyme inhibition

UA is the end product of purine metabolism and is formed from by xanthine oxidase (XO), a multifunctional enzyme responsible for catalyzing the steps of mammalian purine metabolism to convert hypoxanthine to UA [15]. In the process of the converting, XO will produce reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, hydrogen peroxide, etc., that can react with biological macromolecules such as lipids, proteins, and nucleic acids, resulting in the generation of intracellular oxidative stress[16]. Therefore, inhibition of the enzymatic activity of XO is an effective way to reduce UA production. The most important XO enzyme inhibitors are allopurinol, febuxostat, and quercetin, and their modes of action are briefly summarized here.

Allopurinol.

Allopurinol is a purine analog that inhibits XO in the two steps of UA production in which this enzyme is involved: the conversion of hypoxanthine into xanthine acid, and the oxidation of xanthine acid to UA [17]. Allopurinol is converted in the liver to oxipurinol, which has a similar pharmacological effect [17].

Eight clinical trials were statistically analyzed for changes in serum UA concentrations at the end of allopurinol-treated versus control groups. The pooled results showed that the serum UA concentration in the allopurinol treatment group decreased by 2.5 mg/dL compared with the control group, which was statistically significant ($P < 0.001$) [18]. Therefore, allopurinol is one of the important drugs to control UA levels.

Febuxostat.

It also reduces UA production by inhibiting the activity of XO. Unlike allopurinol, febuxostat blocks the molybdenbdenum pterin center of the enzyme, which is more specific than allopurinol [19]. Febuxostat inhibits both oxidized and reduced forms of XO without inhibiting other purine or pyrimidine metabolizing enzymes. In the body, febuxostat is metabolized primarily by uridine diphosphate glucuronosyltransferase, oxidation, and by the CYP isoenzymes 1A2, 2C8, and 2C9 [20].

Compared with allopurinol, febuxostat has shown better results in reducing UA levels, reducing oxidative stress, and reducing the proportion of patients hospitalized for worsening heart failure. It is more suitable for patients who do not have cardiovascular diseases such as atherosclerosis. In addition, febuxostat is thought to have a positive effect on the prognosis of patients with heart failure. Thus, febuxostat may have some advantages in the treatment of patients with hyperuricemia who also have chronic heart failure [21].

Quercetin

Quercetin is a naturally occurring flavonoid compound found in a wide variety of plant foods such as onions, tea, and apples [22]. Its inhibitory effect on XO has been known for a long time [23]. Quercetin inhibits the activity of this enzyme by binding to its active center of XO and changing its three-dimensional structure [24]. Quercetin exerts multiple biological effects due to its anti-inflammatory and antioxidant activity, which may assist in the prevention and treatment of hyperuricemia [25].

2.2. Increasing the excretion of UA

In the metabolic process of purines, the excretion of UA into urine is highly important [26]. This excretion is performed by the kidneys, where UA is removed via a process of filtration, reabsorption, and secretion in the renal tubular system. The excretion of UA can be promoted with drugs that influence these processes [27], some of which are briefly summarized here.

Fenofibrate.

Fenofibrate is most commonly prescribed to treat abnormal blood lipid levels. The effect of fenofibrate on UA excretion is based on its inhibition of UA transporters involved in UA reabsorption in the kidney [28]. Fenofibrate is a relatively small molecule that binds to UA transporters in the renal tubule proximal to the kidney, especially URAT1 and Glucose Transporter 9 (GLUT9). These transporters are normally responsible for the reabsorption of filtered UA in the lumen of the renal tubules back into the bloodstream. Fenofibrate effectively lowers blood UA levels by inhibiting the activity of these transporters, reducing UA reabsorption, and promoting more UA to be excreted in the urine [29,30]. The large Febofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was used to evaluate the effect of the drug on UA levels, which showed effectiveness and lowering of cardiovascular risk (33).

Atorvastatin

Atorvastatin is a statin that is also prescribed to treat abnormal lipid levels. It is able to reduce serum UA levels by increasing UA excretion, as it affects proximal tubular UA reabsorption by acting on an active transport mechanism closely related to sodium ion and tubular reabsorption [31]. This drug, as other lipophilic statins, improves endothelial function and influences the renal vasculature; this increases renal blood flow and improves the glomerular filtration rate, thereby lowering UA levels [32]. However, like other statins, atorvastatin may induce the onset of type 2 diabetes and an increase in visceral adipose tissue in high-risk patients has been observed compared with fenofibrate, so it should be used with caution [33,34].

Benzbromarone and losartan.

Losartan is an angiotensin II receptor antagonist normally prescribed to treat hypertension, but it also inhibits URAT1 [34]. Benzbromarone is used to treat gout as it acts as a nonpurine inhibitor of XO and it also inhibits URAT1, but it has not been approved for use in the United States because of concerns of acute liver injury [13]. Benzbromarone alone is able to reduce plasma UA concentrations and increase UA excretion in patients with Type 2 diabetes [35].

Furosemide, hydrochlorothiazide, and indapamide.

These three drugs are diuretics that promote the excretion of UA by increasing urine output [36]. Furosemide can reduce the reabsorption of UA in the proximal convoluted tubule and inhibit the active transport of UA. Hydrochlorothiazide inhibits the sodium chloride cotransporter (NCC) of the main active chlorine site of the distal convoluted tubule of the renal tubule, thereby reducing sodium and water reabsorption and increasing urine excretion, with increased UA excretion [37]. Indapamide, a thiazide-like diuretic drug, also inhibits NCC leading to its diuretic effect, reducing the reabsorption of UA, and increasing its excretion.

There is some controversy to what extent furosemide and hydrochlorothiazide reduce UA levels. Borghi et al. concluded that thiazides have a greater effect on UA levels and are less conducive to the metabolic health of patients [38]. Huang et al. warned that furosemide may even cause hyperuricemia by worsening kidney function, resulting in an increase in the concentration of UA in the blood [39].

2.3. Drugs with antioxidant effects

UA has an antioxidant effect in the plasma, but when it enters a cell, it behaves as a pro-oxidant and produces reactive oxygen species (ROS) [40]. This dual property explains how UA can be closely related to the onset and development of oxidative damage in susceptible patients, such as chronic kidney disease [41,42]. To counteract this effect, antioxidant medication can reduce oxidative stress caused by high serum levels of UA. Examples include empagliflozin, dapagliflozin and vitamin C.

Empagliflozin and dapagliflozin

Empagliflozin and dapagliflozin are both sodium-glucose transporter 2 (SGLT2) inhibitors they are often prescribed to type 2 diabetes patients. In an experiment with 4304 participants, the estimated glomerular filtration rate (GFR) is 25 to 75 ml/min/1.73 m^2 and the urine albumin/creatinine ratio is 200 to 5000. The primary endpoint event rate is 9.2 % in the dapagliflozin group compared with 14.5 % in the placebo group. The hazard ratio of the dapagliflozin group was 0.61, $P < 0.001$. Thus, dapagliflozin has significant renal and cardiovascular protective effects in patients with chronic kidney disease[43]. UA excretion can be promoted by inducing diabetes with other metabolites and electrolytes [44,45]. Empagliflozin and dapagliflozin may also affect UA levels by reducing the production of inflammatory factors and improving oxidative stress status, and these mechanisms work together to greatly enhance the effectiveness of empagliflozin in lowering UA levels [46].

From a post hoc analysis of the EMPA-REG OUTCOME trial, Ferreira et al. found that empagliflozin reduced serum UA levels and reduced gout flares or the need for anti-gout drugs compared with placebo, in addition to its known cardiovascular and renal benefits. These results provide new possibilities for the clinical application of empagliflozin [47]. However, dapagliflozin is different from empagliflozin in that it has a stronger ability to reduce glycosylated hemoglobin and fasting blood glucose in the treatment of diabetic patients, but the level of HDL cholesterol increased[48]. This means that in clinical use, medical professionals should consider combining the two drugs.

Vitamin C.

High vitamin C intake is significantly associated with low serum UA levels. Vitamin C (ascorbic acid) can reduce UA-induced inflammation and oxidative stress by inhibiting the activation of the nucleotide-binding oligomerization domain, the leucine-rich repeat and the pyrin domain-containing 3 proteins of the inflammasome (Fig. 1) [49,50]. In addition, vitamin C can stimulate UA excretion by the kidneys [51]. Unlike empagliflozin, vitamin C is abundant in certain foods, suggesting that vitamin C intake is a safer and more acceptable way to prevent elevated UA.

3. Improving CHD by reducing UA levels

In patients diagnosed with CHD, there is an independent association between the level of serum UA and the risk of death, and exploring the mechanism(s) behind this association can assist to reduce the impact of UA on CHD with more efficient treatment options.

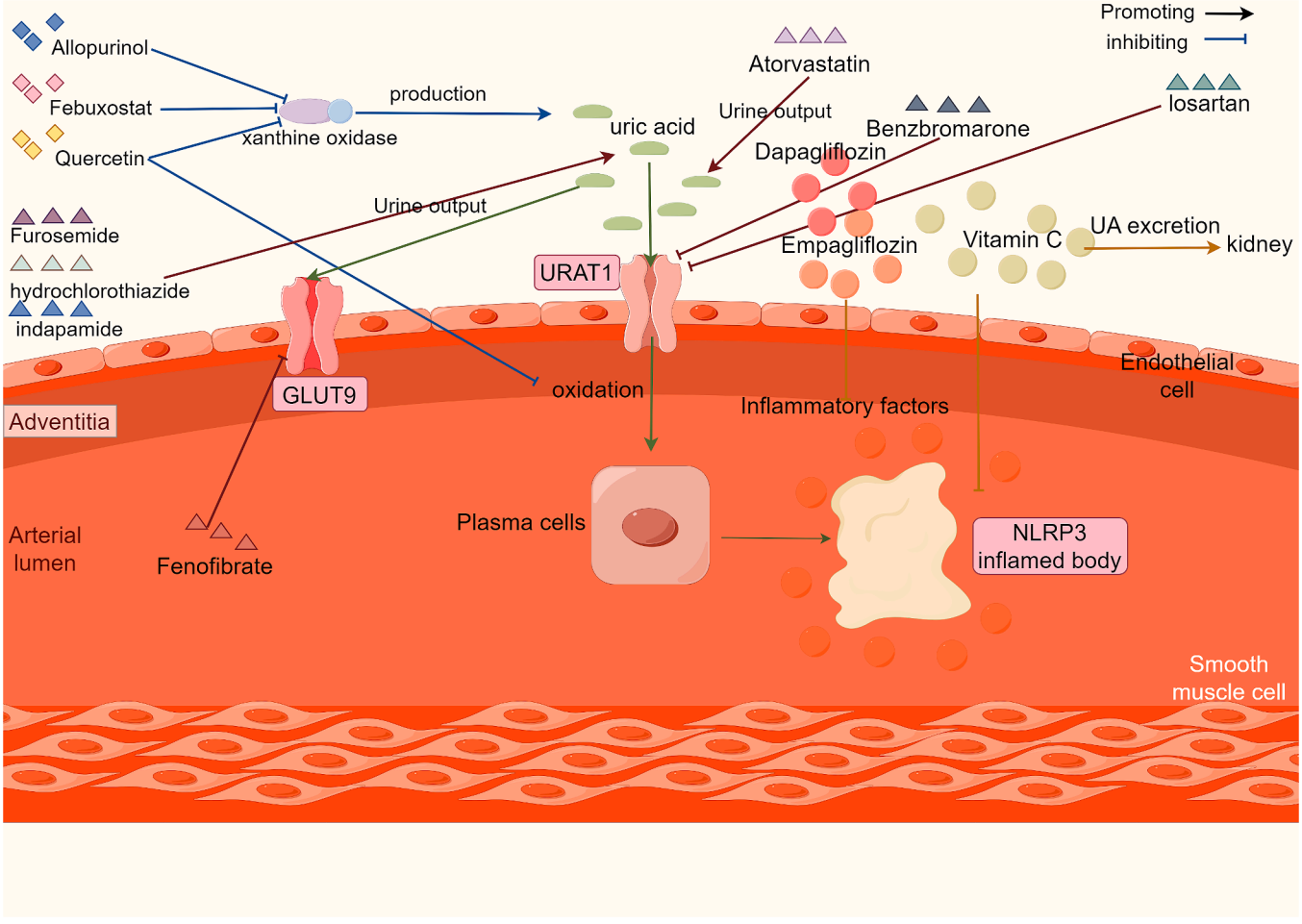

Fig. 1. Schematic diagram of the mechanism of UA level reduction for different drugs. The blue line segment indicates the drug that affects the production of UA. The red line indicates drugs that affect UA excretion. The yellow line indicates the drug that affects the antioxidant effect. The green line segment indicates the transport path of UA in the arterial lumen. Abbreviation: URAT1, uric acid transporter 1; GLUT9, Glucose Transporter 9; NLRP3, Nucleotide- binding oligomerization domain, leucine- rich repeat and pyrin domain- containing 3.

3.1. Reducing coronary atherosclerosis

Elevated UA is involved in the development of multiple cardiovascular diseases, not only CHD but also, hypertension, atrial fibrillation, chronic kidney disease, heart failure, and coronary atherosclerosis [52]. One explanation how hgyperuricemia promotes the occurrence and progression of cardiovascular diseases is by regulating molecular signals involved in inflammatory response, oxidative stress, insulin resistance/diabetes, endoplasmic reticulum stress, and endothelial dysfunction [52]. UA is considered an effective peroxynitrite scavenger in humans, for it can react with peroxynitrite and produce amino carbonyl radicals. The aminocarbonyl radical may be the substance responsible for the increase in peroxynitrite-mediated lipid oxidation. Therefore, UA may increase lipid oxidation under certain conditions[53].

The lipid oxidation is closely related to plaque stability. Oxidative modified lipids and lipoproteins are extremely abundant in the microenvironment of atherosclerotic plaques, and cholesterol crystals are also found in atherosclerotic lesions, which can activate cells to release proinflammatory factors and produce inflammation to affect plaque stability[54]. Except that,elevated serum uric acid (SUA) levels are associated with thinning of the fibrous cap, widening of the mean lipid curvature, reduction of the minimum perfusion area, thin-cap fibro atherosclerotic plaques, micro vessels, macrophages, and cholesterol crystals more frequently in the high UA level group, suggesting that SUA levels were predictors of plaque instability[55]. Therefore, SUA is closely related to plaque stability, and UA-lowering drugs can reduce the occurrence of coronary atherosclerosis by reducing UA levels to reduce vascular endothelial cell damage, oxidative stress, and inflammatory responses.

High levels of UA reduce NO production in lung endothelial cells by enhancing L-arginine-arginase activity, and endothelial dysfunction by decreasing eNOS expression and NO production in human umbilical vein endothelial cells by C-reactive protein or calcium-induced instability of eNOS mRNA [56–59]. Increased oxidative stress then leads to vascular smooth muscle cells (VSMC) proliferation, thickening of vascular walls, apoptosis of endothelial cells (ECs), and increased expression and activity of matrix metalloproteinase (MMPs), which in turn are involved in the establishment of atherosclerotic plaques [56,60].

3.2. Improving myocardial blood supply

The onset of patients with congestive heart failure (CHF) is often accompanied by elevated UA, and many studies and *meta*-analyses have investigated the relationship between UA and morbidity, severity, or prognosis after congestive heart failure [61–67]. For instance, the Framingham O Alisms spring cohort study followed 4912 participants (mean age 36 years at baseline, 52 % women) over 29 years and their incidence of CHF at the highest quartile of UA (>6.3 mg/dl) was nearly 6 times higher than that at the lowest quartile (<3.4 mg/dl) [62]. Congestive heart failure is closely related to myocardial blood supply, atherosclerosis, and endothelial dysfunction. Therefore, reducing, halting or improving the degradation of congestive heart failure due to hypoxia, upregulation of catabolic pathways, insulin resistance, increased cell mortality and tissue wasting rates (especially the development of sarcopenia and cachexia in the end-stage of disease) and impaired renal excretion by lowering UA can be highly beneficial [68,69].

3.3. Improving heart function

Improved heart functions that can be achieved by drug-assisted decreases of UA levels include increased myocardial mechanical function, energy balance and high-energy phosphate concentration, left ventricular ejection fraction, cardiac remodeling, peripheral blood flow, endothelial dysfunction, and reduced natriuretic peptide levels [70–74]. A *meta*-analysis of 6 studies of 1456 patients with heart failure concluded that lowering UA levels in patients with heart failure and high UA levels had a positive effect on cardiac function, resulting in better clinical outcomes [75]. UA reduction therapy with XOR inhibitors such as allopurinol has been widely used to improve outcomes in patients with CHF (Fig. 2), and XOR inhibition has repeatedly shown beneficial effects on this range of cardiac functions [42,71].

4. Strategies for drug use

UA-lowering drugs can UA-lowering drugs can reduce morbidity in patients with CHD, so how to use these drugs rationally becomes the primary issue. The first step is to understand the therapeutic effect of a single drug on the patient, whereby proper medication can reduce the costs of treatment and ensure optimal he treatment effects. There are cases where multiple drugs need to be used to achieve a therapeutic effect, requiring to define the best combination treatment strategy based on the characteristics of the drugs, the patient's situation, the effect-to-risk ratio of the drugs, and the cost of the various drugs currently available. During the course of treatment, patients should be regularly monitored for UA levels, cardiovascular indicators, and allergic reactions, and if needed the treatment regimen should be adjusted in a timely manner.

4.1. Single drug regimens

XOIs such as allopurinol and febuxostat are highly effective in lowering UA levels, and these drugs are relatively well tolerated by most patients and relatively cheap, making them a first choice for chronic treatment [17]. A comparative study between allopurinol and febuxostat reported no significant differences in the primary composite endpoint of these drugs for cardiovascular events, but the risk of cardiovascular and all-cause mortality was significantly increased in the febuxostat group [13,76]. Thus, allopurinol would be the first drug of choice, whereas febuxostat can be used when allopurinol is not tolerated.

Diuretics have also been shown to reduce the incidence of major cardiovascular events in a variety of hypertensive patients while lowering UA. Of the available drugs, indapamide has a smaller immediate response to UA levels after use compared to hydrochlorothiazide, which means that indapamide is relatively more beneficial to the patient's metabolic health and is more suitable for older patients [38].

Among the antioxidant UA-lowering drugs, the SGLT2 inhibitor empagliflozin given at hyperinsulin-euglycemic and hyperglycemic conditions led to a decrease in plasma UA concentration at fasting. Voiding is closely related to urinary glucose excretion and is attenuated during concomitant URAT1 drug blockade. This suggests that empagliflozin and dapagliflozin can induce a decrease in plasma UA concentration and preserve renal function in patients with type 2 diabetes [35]. Empagliflozin also has obvious clinical benefit in reducing UA levels in patients with heart failure [46]. In patients with heart failure and reduced ejection fraction, treated with dapagliflozin had a reduced risk of worsening heart failure or death from cardiovascular causes[77]. Therefore, empagliflozin and dapagliflozin are more suitable for patients with diabetes or heart failure. Vitamin C, on the other hand, is more suitable for daily intake to prevent high levels of UA [51].

4.2. Combination therapies

XOIs can be used in combination with diuretics when the drugs alone are not effective. For patients with impaired renal function, it is recommended to adjust the dose of allopurinol according to creatinine clearance [78]. As reviewed by others comparative studies have shown that thiazide diuretics such as indapamide may be superior to other diuretics for blood pressure control, metabolism, and cardiovascular prophylaxis when combined with ACE inhibitors, and overall, a

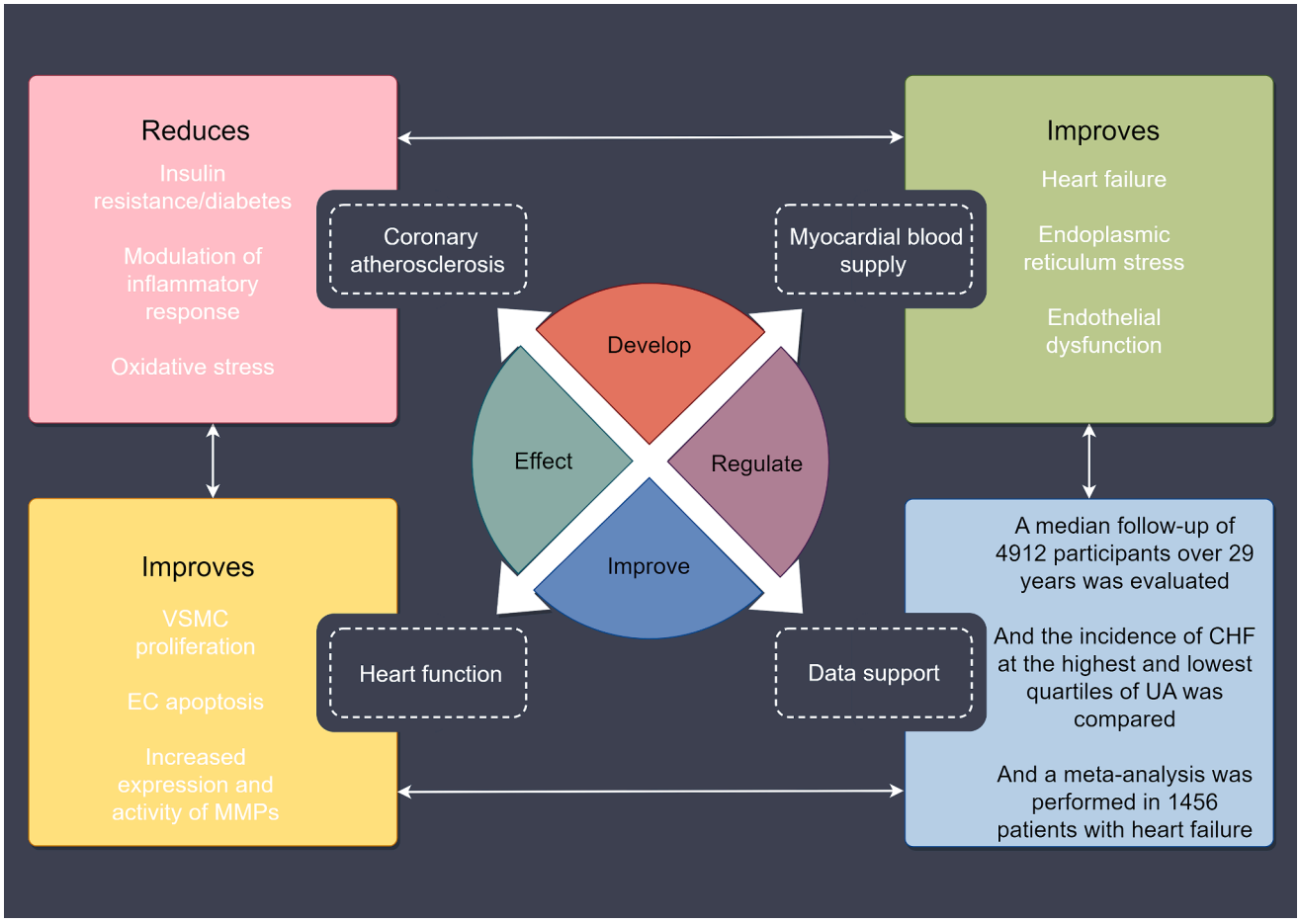

Fig. 2. Improving the mechanisms of CHD by lowering uric acid concentrations as well as the interconnections. Reduces coronary arteriosclerosis. Improves blood supply to the heart muscle. Improves heart function.

combination therapy with ACE inhibitors and diuretics is considered safe, well-tolerated, and effective [38]. For more severe inflammation, it is recommended to add colchicine combination therapy. However, regardless of the symptoms, a personalized medication plan should be developed based on the specific situation of the patient. These strategies can help improve treatment outcomes and reduce the incidence of CHD.

4.3. *Precision medicine*

Allopurinol is preferred in patients with slightly elevated UA levels. Daniel F. B. Wright et al. have developed two tools to predict the therapeutic dose of allopurinol: Easy-Allo1, which is suitable for knowing the pre-treatment blood UA concentration, can support quantitative decision-making. This tool produces unbiased and accurate dose prediction results, Easy-Allo2 Indicated if the pre-treatment blood UA concentration is not known. The prediction of this tool is positively biased, about 70 mg/day overestimated, and the accuracy is also low. Both tools take into account factors that affect the efficacy of allopurinol therapy, such as body weight, baseline blood UA concentration, ethnicity, and renal function (creatinine clearance), and can support a more precise and individualized allopurinol treatment strategy [79]. While UA excretion promoting drugs such as benzbromarone are considered in patients with severe hyperuricemia or severe gout, they are not recommended for patients with renal dysfunction. Nonsteroidal anti-inflammatory drugs or colchicine may be used if inflammation occurs, and interleukin-1 blockers may be considered for patients with frequent indications for colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids [80]. For the development of hypertension, losartan or calcium channel blockers are recommended [81], and for hyperlipidemia, statins or fenofibrate should be considered [82,83]. Low-dose colchicine in patients with a history of coronary artery disease may reduce the incidence of major cardiovascular events [84,85]. If UA level targets cannot be achieved at maximum doses using any available drug and drug combination, pegylase can be added (Fig. 3) [86]. At least for the prevention of CHD in patients with gout. (SEE Fig. 4.).

Although the mechanism and use of UA-lowering drugs for CHD are discussed in the article, some drugs are not recommended for some cardiovascular diseases. For example, in one ALL-HEART trial, there is no difference in the incidence of serious adverse events between allopurinol and usual care, and mortality is also similar between the two groups[87]. In addition, there is no difference in the rate of cancer development between allopurinol-treated and conventional treatment groups. No benefit of allopurinol treatment in other clinical or quality of life is shown except for a lower incidence of gout exacerbations in the allopurinol-treated group. Therefore, in the ALL-HEART trial, allopurinol is not recommended for the secondary prevention of cardiovascular events in patients with ischemic heart disease[87,88].

5. Conclusions and future questions to be addressed

Elevated UA levels are widely recognized as an important risk factor for the development and progression of CHD. Numerous studies have shown that abnormally elevated UA levels may promote the formation of atherosclerosis by altering vascular endothelial cell function, damaging vascular endothelium, and increasing the expression of adhesion molecules. This leads to increased oxidative stress, damaged

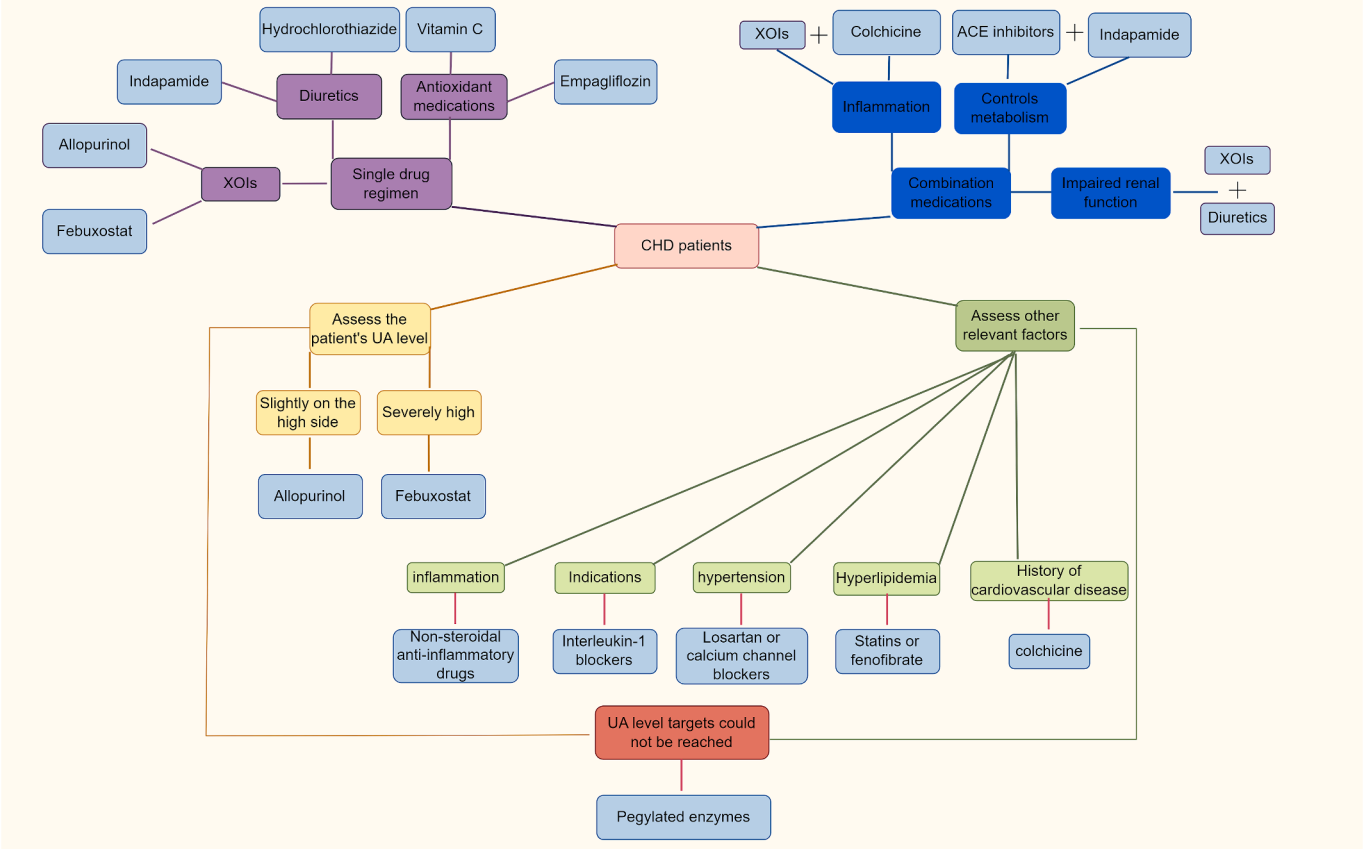

Fig. 3. Summarize the strategy schematic diagram of UA-lowering drugs in clinical application. Single drug regimen. Multiple drugs in combination. Individualized treatment. Light blue text indicates different medications for each situation.

cell membrane structures and function, and induces apoptosis. It promotes inflammatory responses, increases C-reactive protein and cytokine levels, and enhances inflammatory response, affects NO biosynthesis while reducing NO levels, and ultimately leads to endothelial dysfunction. These conditions can induce or contribute to insulin resistance, increasing the risk of diabetes, and indirectly affects cardiovascular health. In addition, myocardial injury and remodeling is aggravated and, left ventricular systolic function can be decreased. This is the context in which appropriate use of UA-lowering drugs has emerged as a potential therapeutic approach. These drugs mainly reduce UA levels by inhibiting the production of UA or promoting its excretion, thereby improving the clinical condition of patients. At present, allopurinol, as a commonly used UA-lowering drug, is recommended as the drug of choice because of its obvious effectivity. Rational use of single drugs or, if needed drug combinations, combined with regular monitoring of the patient's condition, can improve treatment effects and reduce the incidence of CHD.

Although UA-lowering drugs have shown positive preventive effects in clinical practice, there are still many issues that remain to be addressed. First, the specific mechanism of action of these drugs for CHD is not fully understood, and further research is needed to uncover their exact role in cardiovascular protection. Second, individual differences play an important role in treatment responses, so the development of personalized treatment plans and evaluation criteria for different patient groups should be a focus of future research. A normal concentration of UA in serum is generally considered to be below 420 μmol/L for men and less than 360 μmol/L for women. It is important to note that these values may vary depending on age, gender, and other health factors, so the appropriate concentration of UA might slightly differ for different patient populations. In addition, adverse reactions caused by UA-lowering drugs, such as abnormal liver function, skin rash, etc., need to be taken into consideration and deserve more attention and research, in order to better monitor and prevent these potential risks.

Overall, high UA levels can affect CHD by impairing vascular endothelial cell function, increasing oxidative stress, and promoting inflammatory responses. Therefore, it is hoped that medical workers, researchers and patients will work together to identify better prevention and treatment possibilities to deal with high-level UA, as this can provide safer and more effective treatment options for CHD patients.

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CRediT authorship contribution statement

Ruida Cai: Conceptualization, Methodology, Software, Formal analysis, Writing. **Fei Li:** Conceptualization, Funding acquisition, Writing. **Yinhao Li:** Methodology, Writing. **Yue Li:** Methodology, Writing. **Wei Peng:** Methodology, Writing. **Menghui Zhao:** Methodology, Writing. **Mengjun Wang:** Methodology, Writing. **Quanyou Long:** Methodology, Writing. **MengYa Zhu:** Methodology, Writing. **Xiaolin Chen:** Methodology, Writing. **Bing Liu:** Methodology, Writing. **Zhengang Tang:** Methodology, Writing. **Yan Zhang:** Writing. **Xiang Liu:** Conceptualization, Software, Formal analysis, Funding acquisition, Writing. **Feifeng Li:** Methodology, Software, Formal analysis, Funding acquisition, Writing. **Qiong Zhang:** Conceptualization, Software, Formal analysis, Funding acquisition, Writing.

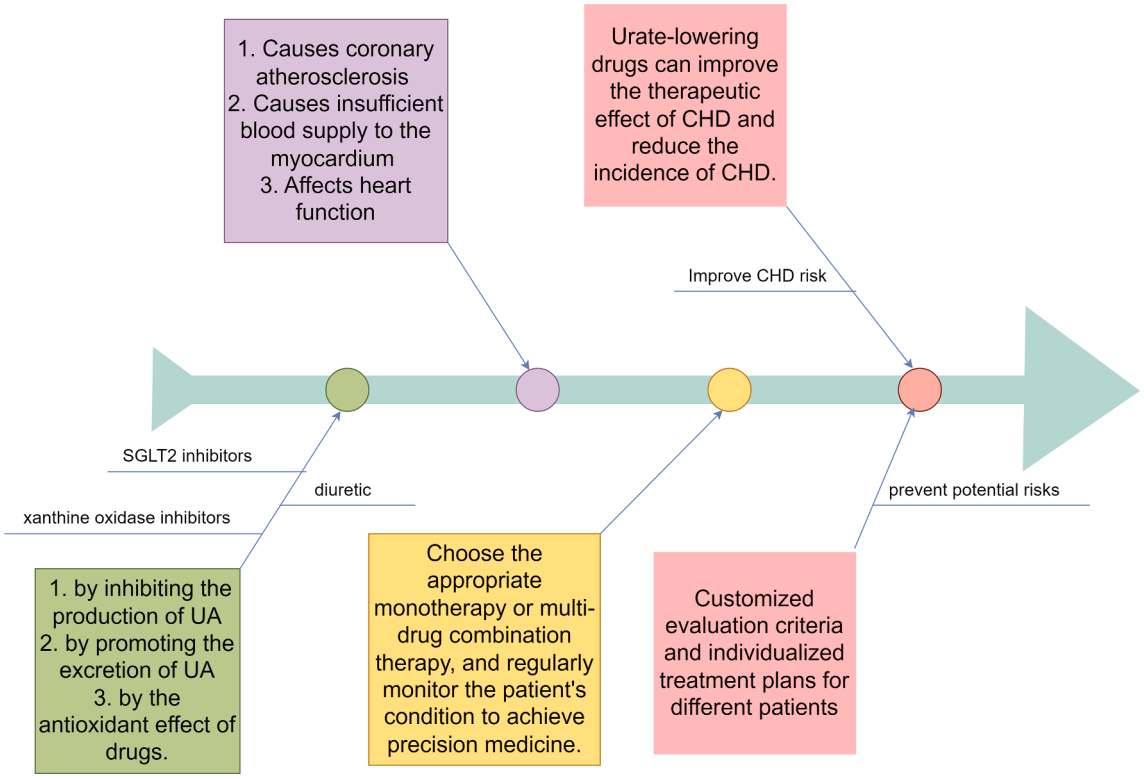

Fig. 4. Summative charts. The green box depicts the mechanism of action of the UA-lowering drug. The purple box depicts that high UA levels affect coronary heart disease through several mechanisms. The yellow box describes the strategy for the use of UA-lowering drugs. The red boxes describe the conclusions and problems that have been asserted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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