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REVIEW

Progress in the treatment of diabetic cardiomyopathy, a systematic review

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Abstract

Diabetic cardiomyopathy (DCM) is a condition characterized by myocardial dysfunction that occurs in individuals with diabetes, in the absence of coronary artery disease, valve disease, and other conventional cardiovascular risk factors such as hypertension and dyslipidemia. It is considered a significant and consequential complication of diabetes in the field of cardiovascular medicine. The primary pathological manifestations include myocardial hypertrophy, myocardial fibrosis, and impaired ventricular function, which can lead to widespread myocardial necrosis. Ultimately, this can progress to the development of heart failure, arrhythmias, and cardiogenic shock, with severe cases even resulting in sudden cardiac death. Despite several decades of both fundamental and clinical research conducted globally, there are currently no specific targeted therapies available for DCM in clinical practice, and the incidence and mortality rates of heart failure remain persistently high. Thus, this article provides an overview of the current treatment modalities and novel techniques pertaining to DCM, aiming to offer valuable insights and support to researchers dedicated to investigating this complex condition.

KEYWORDS
diabetic cardiomyopathy, heart failure, myocardial fibrosis, pharmacotherapy, type 2 diabetes mellitus

Abbreviations: AAV, adeno-associated viral; ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ADA, American Diabetes Association; ADP, adenosine diphosphate; AGE, advanced glycation end product; AMPK, activated protein kinase; ARB, angiotensin II receptor blockers; DCM, diabetic cardiomyopathy; DDR2, discoidin domain receptor 2; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; miRNA, microRNA; MMPs, matrix metalloproteinases; MSC, mesenchymal stem cells; NF-κB, nuclear factor-κB; NO, nitric oxide; N-S, sulfobiguanide; PI3K, phosphatidylinositol-3-kinase; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; S1P, Sphingosine-1-phosphate; SGLT-2, sodium-glucose cotransporter2; SMAD2, small mothers against decapentaplegic2; SphK1, sphingosine kinase 1; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor-beta.

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1 | INTRODUCTION

Diabetes mellitus (DM) is a serious global public health issue, with increasing incidence.[1] Diabetic cardiomyopathy (DCM) is a severe complication characterized by left ventricular diastolic insufficiency with or without left ventricular dilatation, myocardial fibrosis, increased left ventricular weight, ventricular wall thickness, and progression to heart failure, imposing a significant socioeconomic burden.[2,3] Therefore, DCM treatment has become a research focus for many scholars. In addition to diet control and exercise to prevent and treat diabetes, pharmacological treatment is a crucial measure.[4] The pathogenesis of DCM involves metabolic disorders, subcellular component abnormalities, oxidative stress, apoptosis and autophagy, inflammatory response, impaired coronary microcirculation, and altered expression of microRNA (miRNA).[5] Based on current knowledge of DCM pathogenesis, conventional treatment strategies aim to correct glucolipid metabolism disorders, protect cardiomyocytes, and prevent heart failure. However, compared to previous approaches, the latest treatment methods may be more precise and individualized, aiming to intervene in different pathological mechanisms for better treatment outcomes (Figure 1).

2 | RECENT ADVANCES IN TREATMENT RESEARCH

2.1 | Gene therapy

In recent years, as the pathogenesis of DCM has been explored in depth, therapeutic studies targeting the target genes of DCM have emerged.[6] Many studies have shown that miRNAs appear to be aberrantly expressed in DCM, suggesting that miRNAs can be used as early diagnostic methods and therapeutic targets for DCM.[7–11] In recent years, aberrant expression of miR-155 has been regarded as a causative factor in the occurrence of various inflammatory responses and autoimmune diseases.[8–10] MiR-155 exerts its regulatory role in inflammatory responses by inhibiting the expression of the inhibitory factor Bc16 within the nuclear factor-κB (NF-κB) pathway.[9,11] In addition, several studies demonstrate that the downregulation of miR-155, which regulates the transforming growth factor-β (TGF-β1)/Small Mothers Against Decapentaplegic2 (SMAD2) signaling pathway, prevents myocardial fibrosis in DM mice.[11,12] Moreover, miR-30d directly targets FoxO3a to regulate cardiomyocyte pyroptosis in patients with DCM.[13] Research indicates that circ_0071269 directly targets miR-145, leading to the upregulation of gasdermin and modulation of proliferation and pyroptosis in H9c2 cells.[14] Furthermore, cmiR-21 demonstrates significant alterations in expression levels within the heart and circulation following myocardial injury, suggesting a close association with cardiac functional impairments such as myocardial hypertrophy and fibrosis.[15]

Gene editing employs specific gene editing tools to precisely target particular gene mutations or abnormalities, allowing for the repair or correction of gene sequences and the restoration of normal functionality.[16–19] Recent discoveries in novel molecular targets, improved vectors, and delivery methods have significantly enhanced the prospects of gene therapy for cardiovascular diseases.[17,18,20,21] Experimental evidence demonstrates that inhibiting the activation of G protein-coupled estrogen receptor 30 can suppress myocardial fibroblast proliferation in ovariectomized female rats with DM by reducing nitric oxide synthase activity and nitric oxide (NO) levels.[22] The inhibitor of protein phosphatase-1 can enhance the contractility

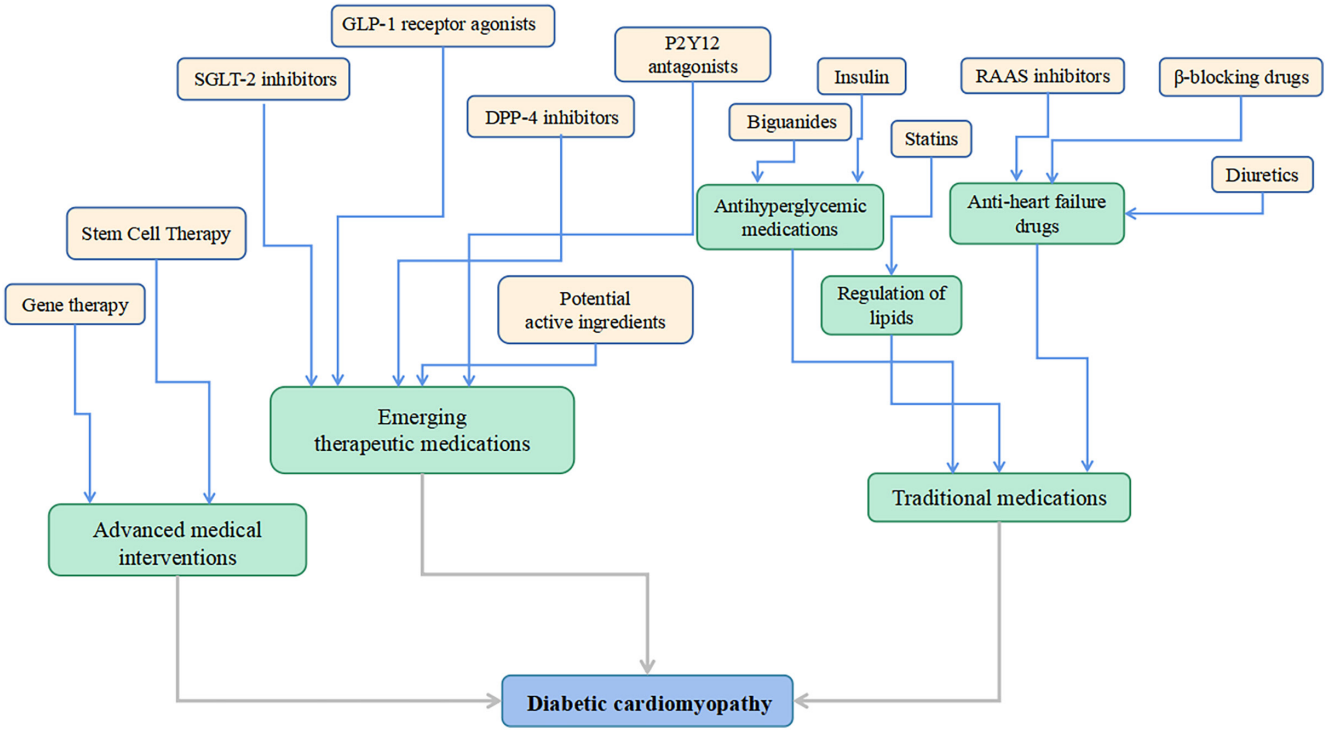

FIGURE 1 Treatments of DCM.

of the left ventricle and left atrium in a pig volume-overloaded heart failure model.[23] Heat shock transcription factor 1 can regulate exercise-induced myocardial angiogenesis post-pressure overload through hypoxia-inducible factor-1 alpha, thereby improving cardiac function in Transverse aortic constriction mice.[24] Research indicates that cardiac C-terminal G protein-coupled receptor kinases2 peptide can inhibit diet-induced adipocyte hypertrophy and insulin resistance, thereby improving myocardial cell metabolism and delaying ventricular remodeling.[25] β-Adrenergic receptors improve cardiac function and delay heart failure progression by inhibiting G protein-coupled receptor kinase 2.[26,27] Specific cardiac myocyte-specific knockout of A Disintegrin. Metalloprotease 17 has been shown to ameliorate left ventricular remodeling and enhance function in mice models of DCM.[28] These findings actively contribute to unraveling the complete mechanisms of gene therapy for DCM and offer potential therapeutic targets. Additionally, cell transduction methods such as retrograde delivery and heart-specific adeno-associated viral (AAV) vectors demonstrate significant long-term efficacy in preclinical models.[16,17,20] However, transitioning successfully from preclinical success to clinical application still faces numerous challenges. The absence of large-scale cardiac clinical trials and the high prevalence of existing antibodies against many AAV serotypes are current issues.[17,20,29] Nevertheless, the novel therapeutic gene, calcium-binding protein S100A1, regulates the Ca^{2+}-related pathway, increases mitochondrial adenosine triphosphate production, enhances energy supply to myocardial cells, and reinforces myocardial cell contractility.[30–32] Experimental evidence indicates that repairing and overexpressing S100A1 in rodent and pig myocardium suggests its potential to improve both systolic and diastolic functions of the heart.[32]

However, gene therapy for DCM is still in its nascent stage, and further extensive research and clinical trials are required to assess its safety and efficacy.[17,18,21] Additionally, gene therapy encounters numerous technical and ethical challenges, including the selection of delivery vectors and the precision of gene editing.[17,21] Consequently, there is currently no widely adopted gene therapy approach for the treatment of DCM in clinical settings.[18]

2.2 | Stem cell therapy

Preliminary research findings suggest that stem cell therapy may hold potential benefits for improving cardiac function, reducing myocardial damage, and enhancing the quality of life for patients.[33,34] Stem cells demonstrate tremendous prospects in cardiac regeneration and the treatment of cardiovascular diseases, including DCM, with mesenchymal stem cells (MSCs) showing particular promise.[35–38] The paracrine effects of MSC-released extracellular vesicles exert a range of beneficial effects on the heart and vasculature, including anti-apoptotic, anti-inflammatory, anti-fibrotic, and pro-angiogenic effects.[33,38] Research has shown that extracellular vesicles derived from MSCs, originating from the stromal fraction of MSCs, mitigate myocardial ischemia–reperfusion injury through modulation of macrophage polarization, specifically regulated by miR-182.[37] Furthermore, extracellular vesicle-mediated delivery of miR-25-3p demonstrates a reduction in myocardial infarction by targeting pro-apoptotic proteins and enhancer of zeste homolog 2.[38]

2.3 | Emerging therapeutic medications

2.3.1 | SGLT-2 inhibitors

In recent years, sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated significant promise in the treatment of DCM.[39–45] Commonly used SGLT-2 inhibitors include empagliflozin, dapagliflozin, and canagliflozin.[39] As opposed to conventional insulin-dependent hypoglycemic medications, SGLT-2 inhibitors work to lower blood glucose by inhibiting SGLT-2R on the renal tubules, reducing glucose reabsorption from the tubules and increasing excretion, and to some extent inhibiting SGLT-1R on the intestine, reducing glucose absorption and utilization in the small intestine to achieve hypoglycemic effects.[39] SGLT-2 inhibitors enable higher urine glucose and sodium excretion, and decreased blood volume in a chronic hyperglycemic setting, lowering cardiac Preload and afterload and raising cardiac output.[40] Studies have shown that dapagliflozin has osmotic diuretic effects in addition to inhibiting myocardial fibroblast activation by blocking the TGF-β/SMAD signaling pathway through activated protein kinase (AMPKα), attenuating streptozotocin (STZ)-induced myocardial fibrosis in rats with DM models, delaying left ventricular remodeling, and enhancing cardiac function.[41] Packer et al. demonstrate that the cytosolic ion exchange protein Na^+-H^+ exchange pump is inhibited, intracellular calcium ions are decreased, myocardial cell injury is reduced, myocardial hypertrophy, fibrosis, and systolic dysfunction are improved. Eventually, the development of heart failure is inhibited.[42] In addition, β-hydroxybutyric acid serves as an efficient metabolic substrate for the heart, and SGLT-2 inhibitors induce β-hydroxybutyric acid production to improve cardiac metabolism at the mitochondrial level in T2DM patients.[42] Moreover, studies have shown that SGLT-2 inhibitors can have a cardioprotective impact by producing uric aciduria and a 10%–15% reduction in plasma uric acid levels by increasing uric acid production and reducing glucose reabsorption through the Human Glucose Transporter 9 transporter.[40] Because SGLT-2 inhibitors are osmotic diuretics, inhibit cardiac Na^+-H^+ exchange, and improve myocardial metabolism, the risk of cardiovascular complications may be reduced in patients with T2DM.[43] Among them, engramine became the first glucose-lowering agent approved by the Food and Drug Administration to reduce cardiovascular mortality in the treatment of T2DM patients with comorbid cardiovascular disease.[44] The relative risk of hospitalization for heart failure in T2DM patients is reduced by 35% after treatment with engramine in the empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes outcome trial; by 33% in the Cardiovascular Assessment of Cargolizine study program; and by 27% in the Dagliflozin Effect cardiovascular events trial.[40,45]

When combined with metformin, SGLT2 inhibitors demonstrate a good safety profile with no increased risk of hypoglycemia and few gastrointestinal adverse effects.[46] The most common adverse effects of SGLT2 inhibitors in clinical practice include glycosuria, genital tract fungal infections, and urinary frequency.[47,48] However, studies have shown that SGLT2 inhibitors may increase the risk of diabetic ketoacidosis (Figure 2).[49–51]

2.3.2 | GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can effectively improve insulin resistance by promoting insulin secretion, inhibiting glucagon secretion, and stimulating islet β-cell proliferation and differentiation. GLP-1 RAs can also effectively control postprandial glucose and body weight by decreasing glucagon secretion, slowing gastric emptying, and reducing food intake.[52] In comparison to insulin, GLP-1 RAs are recommended as the first-injection hypoglycemic therapy of choice for T2DM due to their effectiveness in controlling blood glucose levels without the risk of hypoglycemia, especially in obese patients.[52,53] Several cardiovascular outcome studies have shown that GLP-1 RAs can prevent CV events, and thus, treatment with GLP-1 RAs is recommended specifically for patients with pre-existing atherosclerotic vascular disease.[54,55]

Abnormal expression of type I and III collagen deposition and matrix metalloproteinases (MMPs) are important factors contributing to myocardial fibrosis and diastolic dysfunction.[56] In contrast, GLP-1 RAs activate the AMPK pathway, reduce endoplasmic reticulum stress, and inhibit the expression of type I/III collagen and MMPs, thus improving cardiac function and exhibiting anti-fibrosis properties, which is a new therapeutic direction to prevent or delay the development of DCM.[56,57]

GLP-1 RAs were first approved for the treatment of T2DM in 2005, and the representative drugs are exenatide, liraglutide, and lisinopril.[53] Due to its slow duration of action and short half-life, exenatide, the first approved GLP-1 RA, requires at least two daily injections.[53] Liraglutide, approved in 2009, has an extended half-life of 13 h and is usually effective for glycemic control with once-daily injections.[53] The Cardiovascular Outcomes Assessment trial demonstrates a significant reduction in cardiovascular adverse events and overall mortality in patients with T2DM treated with liraglutide.[57,58] A 52-week randomized controlled trial shows that liraglutide increases left ventricular ejection fraction and significantly improves cardiac function compared to selegiline and glargine insulin treatment.[59]

The most common side effects of GLP-1 RAs are gastrointestinal reactions.[60,61] Among them, semaglutide carries the highest risk of nausea, diarrhea, vomiting, constipation, and pancreatitis, while liraglutide carries the highest risk of upper abdominal pain.[61]

2.3.3 | DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of novel oral antidiabetic medications. They stimulate β-cell growth, proliferation, and differentiation, and promote β-cell secretion by reducing entero-insulin inactivation, increasing the levels of endogenous GLP-1 and glucose-dependent insulinotropic peptide, and prolonging the action of insulin, thereby lowering blood glucose.[60] Additionally, DPP-4 inhibitors inhibit the degradation of Stromal

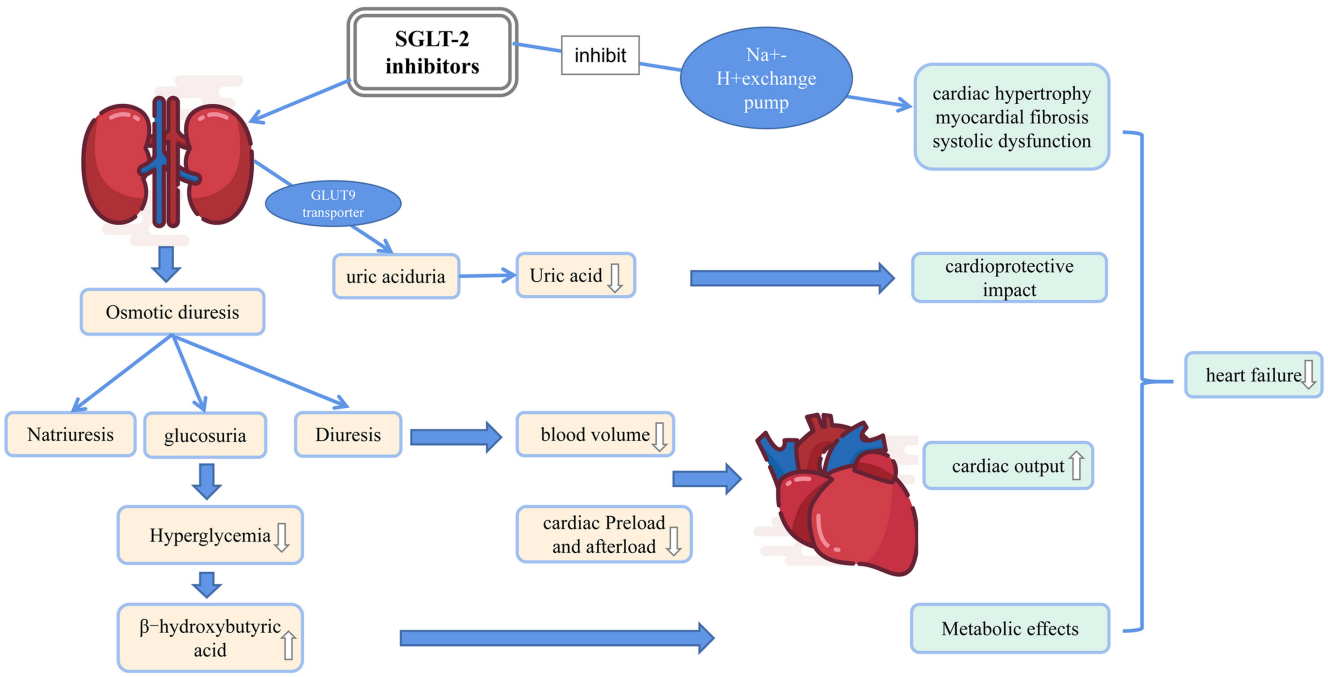

FIGURE 2 The primary mechanisms of action of SGLT-2 inhibitors.

cell-derived factor-1α and enhance the homing of endothelial progenitor cells, which eventually exert vasoprotective effects.[62] Large prospective cardiovascular trials have confirmed that DPP-4 inhibitors do not increase cardiovascular risk and are a safe and effective option for T2DM patients with cardiovascular disease and high-risk factors.[63] Furthermore, in animal experiments, DPP-4 inhibitors have been shown to exert pleiotropic effects on heart failure. Studies have demonstrated that the use of DPP-4 inhibitors is beneficial for the prognosis of patients with diabetes complicated by heart failure.[64,65]

Compared to conventional hypoglycemic agents, DPP-4 inhibitors have a good safety and tolerability profile with no increased risk of hypoglycemia and low gastrointestinal reactions.[66–68] However, a meta-study showed that patients using DPP-4 inhibitors had a significantly increased risk of acute pancreatitis.[69] In addition, some studies have shown that DPP-4 inhibitors can affect the degradation of bradykinin, leading to increased vascular permeability and edema.[70]

2.3.4 | P2Y12 antagonists

P2Y12 antagonists were previously used as the drug of choice for dual antiplatelet therapy in patients with Acute Coronary Syndrome.[71] There are two groups of P2Y12 antagonists in clinical use. The first group is thienotetrahydropyridines or thienopyridines, which includes ticlopidine, clopidogrel, and prasugrel. Ticlopidine is a first-generation thienopyridine that is no longer in clinical use due to toxicity. Clopidogrel, a second-generation thienopyridine, has been the most widely used P2Y12 inhibitor in patients undergoing percutaneous coronary intervention or secondary prevention of ACS.[72] The oral P2Y12 inhibitor Tegretol is more effective than clopidogrel in preventing major cardiovascular events in patients with ACS, but it increases the risk of major bleeding.[73]

Adenosine is a purine nucleoside analog formed by the metabolism of adenosine diphosphate (ADP) or Adenosine triphosphate by nucleotidases released after local tissue hypoxia or tissue injury. Its biological effects include vasodilation, inflammation regulation, and platelet function inhibition.[74] Studies have demonstrated that the P2Y12 receptor antagonist Tegretol exerts its cardioprotective effects mainly by increasing the levels of mesoadenosine.[74] An experiment demonstrates that Tegretol inhibits the activation of NOD-like receptor thermal protein domain associated protein 3 inflammatory vesicles, improves myocardial fibrosis, and slows down the progression of myocardial contractile dysfunction.[75] Meanwhile, the combination of SGLT2 inhibitors dapagliflozin and Tegretol has synergistic effects on the treatment of DCM, slowing myocardial remodeling in DCM in mice with a T2DM model.[75,76]

Patients with DM are at an increased risk of thrombotic events due to the presence of atherosclerosis. Laboratory tests have shown that patients with DCM also have increased blood viscosity.[72,77] P2Y12 receptor antagonists, which inhibit thrombosis by blocking P2Y12 receptor binding and inhibiting platelet glycoprotein IIb/IIIa receptor activation and fibrinogen ligation, can significantly reduce the risk of thrombotic events.[77] Tegretol, on the other hand, inhibits the aggregation of platelets by inducers other than ADP and can inhibit platelet aggregation in vivo in a rapid, efficient, and sustained manner.[77]

In addition to reducing the risk of thrombotic events, studies have shown that P2Y12 receptor antagonists have antitumor effects when P2Y12R or P2Y12R genetic defects are inhibited.[73] However, it should be noted that P2Y12 inhibitors, while antiplatelet coagulation, may increase the risk of exacerbating bleeding.[78]

2.4 | Other medications or potential active ingredients

Sphingosine-1-phosphate (S1P) is a product of the enzyme sphingosine kinase 1 (SphK1).[79–81] Elevated levels of S1P are involved in the process of DCM and myocardial fibrosis.[81,82] A recent study has shown that advanced glycation end product (AGE) inhibitors, in addition to their role in blocking AGE formation, can also prevent DCM by inhibiting the expression of the SphK1 gene.[82] Nicorandil, a microcirculation-improving drug, significantly reduces the risk of cardiovascular events and improves prognosis.[83] It is demonstrated that nicorandil, which activates the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB) pathway, reduces cardiomyocyte apoptosis and improves the symptoms of cardiac insufficiency in DM rats.[84] Moreover, studies have shown that Nesfatin-1 improves insulin sensitivity in STZ-induced DM model rats through the p38-MAPK pathway, reducing inflammation and ameliorating cardiac dysfunction.[85]

In recent years, extensive research has shown that certain herbal extracts have potential therapeutic effects on DCM.[86–91] For instance, Schisandrin B has been found to alleviate DCM by targeting MyD88 and inhibiting MyD88-dependent inflammation.[86] Paeonol promotes OPA1-mediated mitochondrial fusion through the activation of the CK2α-Stat3 pathway, thus mitigating mitochondrial oxidative stress to protect the heart.[87] Piceatannol has also been shown to alleviate inflammation and oxidative stress in high glucose-induced H9C2 cells by modulating the Nrf2/HO-1 and NF-κB pathways.[88] Furthermore, flavonoids have been widely demonstrated to effectively inhibit cell hypertrophy, fibrosis, and apoptosis induced by high glucose.[89,90]

2.5 | Traditional medications

2.5.1 | Conventional antihyperglycemic medications

Classic traditional antihyperglycemic medications include insulin and metformin, among others (Figure 3). Insulin is the first-line agent for the treatment of type 1 diabetes mellitus (T1DM), as it is the only

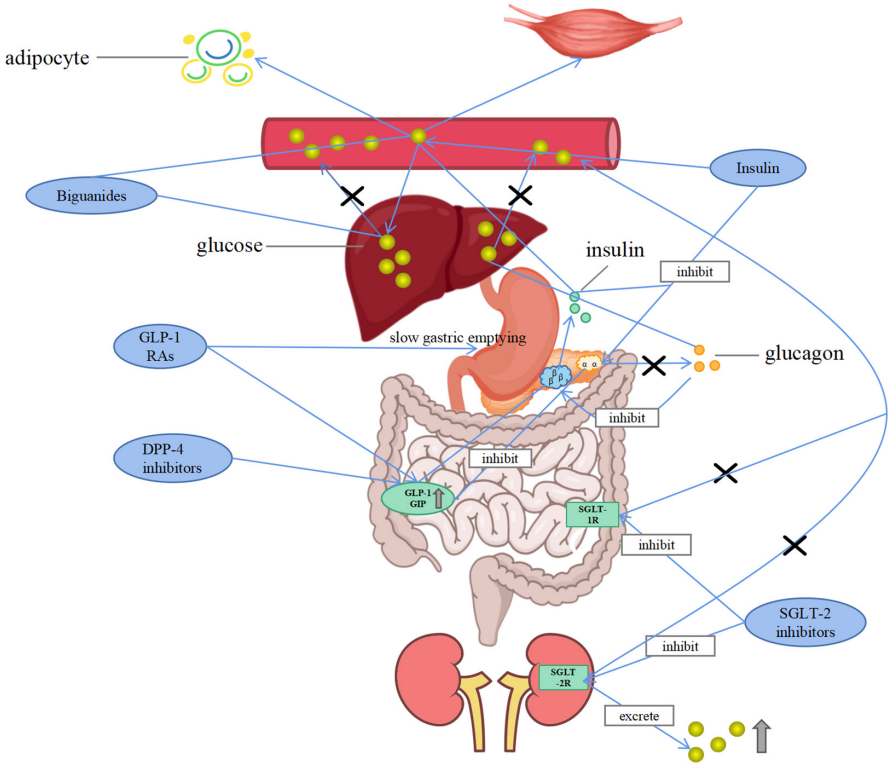

FIGURE 3 Mechanisms of blood glucose regulation.

hypoglycemic hormone in the body.[92] Diabetic patients experience disturbances in sugar and fat metabolism, leading to an excessive accumulation of glucose and lipids. This disrupts the balance of myocardial energy-redox, impairs mitochondrial function, and increases the generation of reactive oxygen species (ROS), triggering oxidative stress in cardiac cells. Insulin effectively manages blood sugar levels, suppresses mitochondrial ROS production, upregulates intracellular antioxidant enzymes, and mitigates excessive ROS, thus reducing damage to myocardial cells, and delaying ventricular remodeling.[93,94] Insulin can also inhibit the transcription of transcription factor signal transducer and activator of transcription and the activation of the interleukin-6 signaling pathway, by regulating the extracellular regulated protein kinase pathway and PI3K/forkhead box O1 pathway to reduce the production of inflammatory mediators, ultimately attenuating the myocardial inflammatory response.[95,96] Secondly, insulin improves cardiac metabolism by promoting glucose uptake and utilization by cardiomyocytes and reducing free fat acid accumulation. In addition, insulin can participate in myocardial contraction and prevent ischemia-induced apoptosis and autophagy directly or indirectly through insulin-like growth factors-1.[95] It has been shown that the combination of insulin and selenium synergistically resists apoptosis in DM cardiomyocytes by regulating Ku70 acetylation and inhibiting Bax translocation.[96]

Metformin has become the gold standard in the treatment of diabetes in several countries due to its beneficial effects on the treatment of other underlying metabolic diseases in addition to its effective hypoglycemic effect.[97,98] The American Diabetes Association (ADA) recommends pharmacological treatment with metformin first, and if the drug alone is not effective in controlling blood glucose, it is used in a diphasic or triple combination.[99]

In addition to its effective hypoglycemic effect, experimental studies on DM model mice demonstrate that metformin, as an AMPK agonist, could inhibit cardiomyocyte apoptosis by activating AMPK, improving autophagy, and activating the prokineticin2/prokinetic receptor-mediated PKB/glycogen synthase kinase-3β signaling pathways, increasing NO bioavailability, and reducing advanced glycated end-products deposition.[99–101] Meanwhile, the mitochondrial respiratory chain is improved, mitochondrial uncoupling, increases energy production is reduced, myocardial diastolic efficiency is strengthened, and the process of cardiac remodeling is slowed by activating the AMPK pathway.[100] The Discoidin Domain Receptor 2 (DDR2), as a collagen receptor tyrosine kinase, plays a specific regulatory role in the expression of type I collagen genes in cardiac and vascular adventitial fibroblasts.[102–104] Research has shown that metformin attenuates the increased expression of DDR2 mRNA and protein induced by high glucose by inhibiting the TGF-β1/SMAD2/3 signaling pathway.[104] Additionally, it inhibits the expression of fibronectin and type I collagen dependent on DDR2, thus slowing down the progression of myocardial fibrosis and ventricular remodeling.[103,104]

A multicenter, double-blind, placebo-controlled study shows a 24% incidence of gastrointestinal reactions to metformin at 1000 mg/day as starting therapy.[105] In addition, metformin is prone to accumulate in patients with moderate to severe chronic kidney disease, leading to lactic acidosis, central nervous system dysfunction, cardiovascular failure, renal failure, and even death.[97]

2.5.2 | Statins

Patients with DM often exhibit increased lipid levels.[106] Therefore, reducing lipid levels is crucial for the prevention and treatment of cardiovascular disease. Statins are effective inhibitors of cholesterol biosynthesis and the most effective drugs for reducing low-density lipoprotein cholesterol, which is essential for primary and secondary prevention of coronary heart disease and lowering cardiovascular morbidity and mortality rates.[107] As the preferred lipid-modifying drug, statins have been shown to improve cardiovascular prognosis in patients with DM and are often used for cardiovascular disease prevention in patients with T2DM. They also have the added benefit of reducing inflammatory responses and improving vascular endothelial function while effectively lowering total cholesterol levels.[108] Major guidelines for cardiovascular disease prevention agree that patients with DM and diagnosed cardiovascular disease are at high risk for future atherosclerotic cardiovascular disease and require intensive lipid regulation and lipid-lowering.[109]

Patients with DCM are susceptible to myocardial inflammatory responses due to the hyperglycemic environment in the body, which is closely related to the development of vascular endothelial dysfunction.[110] Studies have shown that statins can inhibit the activation of the inflammatory factor interleukin-1, reduce the myocardial inflammatory response in DCM patients, and improve endothelial dysfunction, thereby playing a myocardial protective role.[110,111]

Statins are generally well-tolerated, but their side effects are mainly related to the dose taken. When the dose is increased to 40 mg or even 80 mg, liver damage characterized by elevated transaminases and rhabdomyolysis characterized by elevated creatine kinase may occur.[112]

2.5.3 | Anti-heart failure drugs

Patients with DCM often develop heart failure in the middle to late stages of DM development. In addition to glycemic control, anti-heart failure drugs can be used.

2.5.4 | Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system (RAAS) inhibitors are divided into angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and direct renin inhibitors. ACEI and ARB are first-line treatments for cardiovascular disease in patients with DM.[113] RAAS inhibitors have been shown to inhibit the development of inflammatory and fibrotic responses and improve cardiovascular systolic and diastolic responses in patients with cardiovascular disease.

RAAS inhibitors function as hypotensive agents by inhibiting Ang II synthesis, leading to a reduction in ventricular diastolic pressure and the treatment of congestive heart failure.[114] Additionally, RAAS inhibitors can inhibit myocardial remodeling through various pathways, potentially providing a protective effect on DCM.[114,115] Experimental studies suggest that RAAS inhibitors may prevent DCM by inhibiting cardiac-specific NF-κB signaling.[116] A study finds that Alamandine, the newest identified peptide of the renin-angiotensin system, attenuates myocardial oxidative stress and inflammatory responses and prevents myocardial lesions in a DM mouse model.[117] Captopril, an ACEI inhibitor, improved end-diastolic pressure elevation and inhibited myocardial fibrosis in spontaneous DM rats after treatment for 4 months, thus playing a preventive role in DCM.[118]

Although ACEIs are generally well-tolerated and have no significant immediate side effects, some studies suggest that reducing Ang II production may lead to adverse effects such as hypotension, acute renal failure, and hyperkalemia.[119] Increased vascular permeability and interstitial fluid accumulation, typically caused by bradykinin, may cause side effects such as cough, angioedema, and anaphylactic-like reactions. Moreover, side effects such as hypotension, early renal decline, renal insufficiency, and hyperkalemia are associated with drug doses.[119,120]

2.5.5 | β-Blocking drugs

β-Blocking drugs are indispensable for treating heart failure patients with reduced ejection fraction.[121] β-Blocking drugs can reduce myocardial oxygen consumption, improve cardiac metabolism, and attenuate myocardial fibrosis, leading to reduced mortality in heart failure. These drugs inhibit cardiomyocyte β1 receptors, decrease the rate of lipolysis by inhibiting adipose β3 receptors, and reduce glycogenolysis by inhibiting the hyperglycemic response induced by adrenaline, thereby lowering blood glucose. Additionally, numerous recent studies have demonstrated that carvedilol improves myocardial hypertrophy, oxidative stress-induced cardiomyocyte apoptosis, and myocardial fibrosis, ameliorating ventricular remodeling and cardiac dysfunction and reducing mortality in heart failure.[122]

The use of β-blockers is effective against angina pectoris and hypertension. In secondary prevention, they can improve patients with previous myocardial infarction or left ventricular systolic dysfunction, as well as reduce mortality.[123] However, side effects of β-blockers include increased insulin resistance, dyslipidemia, new-onset DM, and weight gain.[124] In addition, β-blockers have a relatively high incidence of stroke and cardiovascular mortality.[124]

2.5.6 | Diuretics

The ADA recommends thiazide diuretics for the treatment of DM patients with combined hypertension. Diuretics control blood volume,

lower blood pressure, prevent cardiovascular disease with long-term use, and reduce morbidity and mortality.[125] Patients with DCM without reduced ejection fraction who have water retention can improve edema with diuretics such as spironolactone. Liu W et al. treated STZ-induced DM model rats with spironolactone for 12 weeks and found that myocardial oxidative stress and inflammatory response were reduced, and myocardial fibrosis was improved by spironolactone.[126] In addition, patients with chronic heart failure are often treated with circulating diuretics to control congestive symptoms.[127]

However, the overuse of diuretics can cause reduced tissue perfusion, renal impairment, water-electrolyte disturbances, and occasionally gastrointestinal symptoms.[127,128]

Therapeutic medications	Advantages	Disadvantages
Emerging therapeutic medications		
SGLT-2 inhibitors	• Increase urinary glucose excretion for glycaemic control • Weight loss • Blood pressure reduction • Low risk of hypoglycaemia • Few gastrointestinal adverse effects • Improvement of cardiac metabolism • Enhancing cardiac function • Anti-myocardial fibrosis • Reduce cardiovascular event risk	• Osmotic diuresis, possible risk of hypotension and falls • Association with genital and possibly urinary tract infections • Small increased risk of diabetic ketoacidosis
GLP-1 receptor agonists	• Glucose dependent increase in insulin secretion and inhibition of glucagon secretion for glycaemic control • Weight loss • Low risk of hypoglycaemia • Possible effect on β-cell survival • Anti-myocardial fibrosis • Reduce cardiovascular adverse events • improvement of cardiac function	• Gastrointestinal adverse effects • Possible increased risk of pancreatitis
DPP-4 inhibitors	• Glucose dependent increase in insulin secretion and inhibition of glucagon secretion for glycaemic control • Low risk of hypoglycaemia • Possible benefit on β-cell survival • Few gastrointestinal adverse effects • Cardiovascular protective effect • Improve prognosis of diabetes-related heart failure	• Increased risk of pancreatitis • Possible increased vascular permeability and edema
P2Y12 antagonists	• Improvement of myocardial fibrosis • Delay in myocardial contractile dysfunction • Reduction in thrombotic event risk	• Potential increased risk of exacerbation
Potential active ingredients	• Multi-pathway safeguarding of myocardial cells, involving reduction in oxidative stress and myocardial cell apoptosis	• Unknown long-term safety • Lack of large-scale clinical trial study results
Traditional medications		
Biguanides	• Effective hypoglycemic effect • Good long-term safety • Low risk of hypoglycaemia • Inhibition of cardiomyocyte apoptosis • Alleviation of cardiac remodeling • Anti-myocardial fibrosis	• Gastrointestinal adverse effects • Multiple possible contraindications, especially renal impairment and hypoxaemia
Insulin	• Sustained glycaemic improvements • Improvement of cardiac metabolism • Inhibition of cardiomyocyte apoptosis • Alleviation of cardiac remodeling	• Weight gain • Hypoglycaemia • Fluid retention
Statins	• Cardiovascular protective effect • Mitigation of myocardial inflammatory response	• Dose-related liver injury and rhabdomyolysis
RAAS inhibitors	• Blood pressure reduction • Anti-myocardial fibrosis • Reduction in oxidative stress • Mitigation of myocardial inflammatory response • Delay in myocardial contractile dysfunction • Alleviation of cardiac remodeling	• Potential causes of hypotension, renal dysfunction, and hyperkalemia
β-blocking drugs	• Blood pressure reduction • Anti-myocardial fibrosis • improvement of cardiac function • Alleviation of cardiac remodeling • Improvement of cardiac metabolism	• Insulin resistance • Lipid abnormalities • Incident diabetes • Weight gain • Potential increased risk of stroke • Elevated cardiovascular mortality
Diuretics	• Blood pressure reduction • Spironolactone can reduce myocardial oxidative stress and inflammatory response • Cardiovascular protective effect	• Renal impairment • Electrolyte imbalance • Occasional gastrointestinal symptoms
Advanced medical interventions		
Gene therapy	• Fundamentally obstructing or reversing the pathological process • Significant therapeutic efficacy	• Lack of large-scale clinical trials to validate its safety and efficacy • Potential unknown risks • Technical and ethical challenges
Stem Cell Therapy	• Assistance in cardiomyocyte self-repair • Significant therapeutic efficacy	• Lack of large-scale clinical trials to validate its safety and efficacy

FIGURE 4 The current advantages and disadvantages of DCM treatments.

3 | COMPARISON OF EMERGING INTERVENTION MEASURES WITH EXISTING THERAPIES

Emerging intervention measures, such as gene therapy and stem cell therapy, are novel treatment approaches developed based on existing therapies.[18,19,33,34] They aim to delve into the pathological mechanisms and pathogenesis of DCM, striving for improved treatment outcomes.[129,130]

First, emerging intervention measures place greater emphasis on the pathogenesis of DCM, attempting to fundamentally block or reverse pathological processes.[19,21,129,130] Compared to existing therapies, these new treatment methods may more precisely target relevant pathological and physiological processes, leading to more pronounced treatment effects.[18,19,33,113,130,131] Second, emerging intervention measures may focus more on individualized treatment. At present, the current therapeutic strategies for DCM primarily center around glycemic control, blood pressure management, lipid regulation, and symptomatic relief.[130,132,133] But they cannot directly intervene at the genetic level.[132] Gene therapy's advantage lies in its ability to intervene in the root cause of the disease, potentially achieving long-term and personalized treatment effects.[18,19,33–36,129]

Existing therapies mainly rely on drug management and symptom relief to control disease progression, but they cannot facilitate the recovery of damaged myocardium.[33,113,131] In contrast, stem cell therapy holds potential for regeneration and repair, aiding in the self-repair of myocardial cells and improving cardiac function.[33–36,131]

It should be noted that the field of DCM treatment is still evolving, and emerging intervention measures are still in the research stage, requiring clinical trials to validate their safety and effectiveness.[16–18,132] For patients with DCM, current existing therapies remain essential for management (Figure 4).

4 | CONCLUSION

DCM has attracted widespread attention as an independent disease in recent years. Effective glycemic control, regulation of blood pressure, lipids, and other risk factors, as well as protection of cardiomyocytes, are the main treatment strategies at present. The emerging therapeutic drugs demonstrate unique advantages in treating DCM, protecting the heart, delaying myocardial remodeling, and reducing adverse reactions. However, certain more personalized, targeted treatments have yet to undergo large-scale clinical trials to validate their safety and efficacy. The future treatment of DCM needs to be based on a full understanding of its pathological mechanisms and more precise and effective therapeutic approaches for its target genes.

AUTHOR CONTRIBUTIONS

Yiyi Shou, Aqiong Xie, and Xingyu Li drafted the manuscript. Quan Fang, Xinyan Fu, and Yinghong Zhang helped to prepare and revise the manuscript. Wenyan Gong, Xingwei Zhang, Mingwei Wang, and Dong Yang were involved in revising it critically. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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All supporting data and material are available within the article.

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Not applicable.

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REFERENCES

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. 2011;94(3):311-321. doi:10.1016/j.diabres.2011.10.029
2. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol*. 1972;30(6):595-602. doi:10.1016/0002-9149(72)90595-4
3. Gong W, Jiao Q, Yuan J, et al. Cardioprotective and anti-inflammatory effects of Caveolin 1 in experimental diabetic cardiomyopathy. *Clin Sci (Lond)*. 2023;137(6):511-525. doi:10.1042/CS20220874
4. Wang H, Bei Y, Lu Y, et al. Exercise prevents cardiac injury and improves mitochondrial biogenesis in advanced diabetic

cardiomyopathy with PGC-1α and Akt activation. *Cell Physiol Biochem*. 2015;35(6):2159-2168. doi:10.1159/000374021
5. Nakamura K, Miyoshi T, Yoshida M, et al. Pathophysiology and treatment of diabetic cardiomyopathy and heart failure in patients with diabetes mellitus. *Int J Mol Sci*. 2022;23(7):3587. doi:10.3390/ijms23073587
6. Joladarashi D, Zhu Y, Willman M, et al. STK35 gene therapy attenuates endothelial dysfunction and improves cardiac function in diabetes. *Front Cardiovasc Med*. 2022;8:798091. doi:10.3389/fcvm.2021.798091
7. Chandrasekera D, Katare R. Exosomal microRNAs in diabetic heart disease. *Cardiovasc Diabetol*. 2022;21(1):122. doi:10.1186/s12933-022-01544-2
8. Wen Q, Wang Y, Pan Q, et al. MicroRNA-155-5p promotes neuroinflammation and central sensitization via inhibiting SIRT1 in a nitroglycerin-induced chronic migraine mouse model. *J Neuroinflammation*. 2021;18(1):287. doi:10.1186/s12974-021-02342-5
9. Chen M, Wang F, Xia H, Yao S. MicroRNA-155: regulation of immune cells in sepsis. *Mediators Inflamm*. 2021;2021:8874854. doi:10.1155/2021/8874854
10. Jankauskas SS, Gambardella J, Sardu C, Lombardi A, Santulli G. Functional role of miR-155 in the pathogenesis of diabetes mellitus and its complications. *Noncoding RNA*. 2021;7(3):39. doi:10.3390/ncrna7030039
11. Lin B, Zhao H, Li L, et al. Sirt1 improves heart failure through modulating the NF-κB p65/microRNA-155/BNDF signaling cascade. *Aging*. 2020;13(10):14482-14498. doi:10.18632/aging.103640
12. Zhang D, Cui Y, Li B, Luo X, Li B, Tang Y. MiR-155 regulates high glucose-induced cardiac fibrosis via the TGF-β signaling pathway. *Mol Biosyst*. 2016;13(1):215-224. doi:10.1039/c6mb00649c
13. Li J, Sha Z, Zhu X, et al. Targeting miR-30d reverses pathological cardiac hypertrophy. *EBioMedicine*. 2022;81:104108. doi:10.1016/j.ebiom.2022.104108
14. Fu L, Zhang J, Lin Z, Li Y, Qin G. CircularRNA circ_0071269 knockdown protects against from diabetic cardiomyopathy injury by microRNA-145/gasdermin a axis. *Bioengineered*. 2022;13(2):2398-2411. doi:10.1080/21655979.2021.2024688
15. Surina S, Fontanella RA, Scisciola L, Marfella R, Paolisso G, Barbieri M. miR-21 in human cardiomyopathies. *Front Cardiovasc Med*. 2021;8:767064. doi:10.3389/fcvm.2021.767064
16. Pajula J, Lähteenvuo J, Lähteenvuo M, et al. Adenoviral VEGF-DΔNΔC gene therapy for myocardial ischemia. *Front Bioeng Biotechnol*. 2022;10:999226. doi:10.3389/fbioe.2022.999226
17. Schwartze J, Havenga M, Bakker W, Bradshaw A, Nicklin S. Adenoviral vectors for cardiovascular gene therapy applications: a clinical and industry perspective. *J Mol Med (Berl)*. 2022;100(6):875-901. doi:10.1007/s00109-022-02208-0
18. Kieserman JM, Myers VD, Dubey P, Cheung JY, Feldman AM. Current landscape of heart failure gene therapy. *J Am Heart Assoc*. 2019;8(10):e012239. doi:10.1161/JAHA.119.012239
19. Zhang B. CRISPR/Cas gene therapy. *J Cell Physiol*. 2021;236(4):2459-2481. doi:10.1002/jcp.30064.E
20. Bera A, Sen D. Promise of adeno-associated virus as a gene therapy vector for cardiovascular diseases. *Heart Fail Rev*. 2017;22(6):795-823. doi:10.1007/s10741-017-9622-7
21. Hulot JS, Ishikawa K, Hajjar RJ. Gene therapy for the treatment of heart failure: promise postponed. *Eur Heart J*. 2016;37(21):1651-1658. doi:10.1093/eurheartj/ehw019
22. Wang X, Tan Y, Xu B, et al. GPR30 attenuates myocardial fibrosis in diabetic Ovariectomized female rats: role of iNOS signaling. *DNA Cell Biol*. 2018;37(10):821-830. doi:10.1089/dna.2018.4208
23. Watanabe S, Ishikawa K, Fish K, et al. Protein phosphatase inhibitor-1 gene therapy in a swine model of nonischemic heart failure. *J Am Coll Cardiol*. 2017;70(14):1744-1756. doi:10.1016/j.jacc.2017.08.013
24. Tian X, Zhou N, Yuan J, et al. Heat shock transcription factor 1 regulates exercise-induced myocardial angiogenesis after pressure overload via HIF-1α/VEGF pathway. *J Cell Mol Med*. 2020;24(3):2178-2188. doi:10.1111/jcmm.14872
25. Manaserh IH, Bledzka KM, Junker A, Grondolsky J, Schumacher SM. A cardiac amino-terminal GRK2 peptide inhibits maladaptive adipocyte hypertrophy and insulin resistance during diet-induced obesity. *JACC Basic Transl Sci*. 2022;7(6):563-579. doi:10.1016/j.jacbts.2022.01.010
26. Zhai R, Varner EL, Rao A, et al. Myocardial GRK2 reduces fatty acid metabolism and β-adrenergic receptor-mediated mitochondrial responses. *Int J Mol Sci*. 2022;23(5):2777. doi:10.3390/ijms23052777
27. Pfleger J, Gross P, Johnson J, et al. G protein-coupled receptor kinase 2 contributes to impaired fatty acid metabolism in the failing heart. *J Mol Cell Cardiol*. 2018;123:108-117. doi:10.1016/j.yjmcc.2018.08.025
28. Xue F, Cheng J, Liu Y, et al. Cardiomyocyte-specific knockout of ADAM17 ameliorates left ventricular remodeling and function in diabetic cardiomyopathy of mice. *Signal Transduct Target Ther*. 2022;7(1):259. doi:10.1038/s41392-022-01054-3
29. Issa SS, Shaimardanova AA, Solovyeva VV, Rizvanov AA. Various AAV serotypes and their applications in gene therapy: an overview. *Cell*. 2023;12(5):785. doi:10.3390/cells12050785
30. Katz MG, Gubara SM, Hadas Y, et al. Effects of genetic transfection on calcium cycling pathways mediated by double-stranded adeno-associated virus in postinfarction remodeling. *J Thorac Cardiovasc Surg*. 2020;159(5):1809-1819.e3. doi:10.1016/j.jtcvs.2019.08.089
31. Sanganalmath SK, Dubey S, Veeranki S, Narisetty K, Krishnamurthy P. The interplay of inflammation, exosomes and Ca^{2+} dynamics in diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2023;22(1):37. doi:10.1186/s12933-023-01755-1
32. Pleger ST, Shan C, Ksienzyk J, et al. Cardiac AAV9-S100A1 gene therapy rescues post-ischemic heart failure in a preclinical large animal model. *Sci Transl Med*. 2011;3(92):92ra64. doi:10.1126/scitranslmed.3002097
33. Xiong J, Hu H, Guo R, Wang H, Jiang H. Mesenchymal stem cell exosomes as a new strategy for the treatment of diabetes complications. *Front Endocrinol (Lausanne)*. 2021;12:646233. doi:10.3389/fendo.2021.646233
34. Chen F, Li X, Zhao J, Geng J, Xie J, Xu B. Bone marrow mesenchymal stem cell-derived exosomes attenuate cardiac hypertrophy and fibrosis in pressure overload induced remodeling. *In Vitro Cell Dev Biol Anim*. 2020;56(7):567-576. doi:10.1007/s11626-020-00481-2
35. Zhang YQ, Hong L, Jiang YF, et al. hAECs and their exosomes improve cardiac function after acute myocardial infarction in rats. *Aging*. 2021;13(11):15032-15043. doi:10.18632/aging.203066
36. Shi Y, Yang Y, Guo Q, et al. Exosomes derived from human umbilical cord mesenchymal stem cells promote fibroblast-to-myofibroblast differentiation in inflammatory environments and benefit cardioprotective effects. *Stem Cells Dev*. 2019;28(12):799-811. doi:10.1089/scd.2018.0242
37. Zhao J, Li X, Hu J, et al. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. *Cardiovasc Res*. 2019;115(7):1205-1216. doi:10.1093/cvr/cvz040
38. Peng Y, Zhao JL, Peng ZY, Xu WF, Yu GL. Exosomal miR-25-3p from mesenchymal stem cells alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2. *Cell Death Dis*. 2020;11(5):317. doi:10.1038/s41419-020-2545-6
39. Huang K, Luo X, Liao B, Li G, Feng J. Insights into SGLT2 inhibitor treatment of diabetic cardiomyopathy: focus on the mechanisms. *Cardiovasc Diabetol*. 2023;22(1):86. doi:10.1186/s12933-023-01816-5

40. Kluger AY, Tecson KM, Lee AY, et al. Class effects of SGLT2 inhibitors on cardiorenal outcomes. *Cardiovasc Diabetol*. 2019;18(1):99. doi:10.1186/s12933-019-0903-4
41. Tian J, Zhang M, Suo M, et al. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPKα/TGF-β/Smad signalling in type 2 diabetic rats. *J Cell Mol Med*. 2021;25(16):7642-7659. doi:10.1111/jcmm.16601
42. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol*. 2017;2(9):1025-1029. doi:10.1001/jamacardio.2017.2275
43. Sørensen MH, Bojer AS, Jørgensen NR, et al. Fibroblast growth factor-23 is associated with imaging markers of diabetic cardiomyopathy and anti-diabetic therapeutics. *Cardiovasc Diabetol*. 2020;19(1):158. doi:10.1186/s12933-020-01135-z
44. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1
45. McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail*. 2019;21(5):665-675. doi:10.1002/ejhf.1432
46. Avogaro A, Delgado E, Lingvay I. When metformin is not enough: pros and cons of SGLT2 and DPP-4 inhibitors as a second line therapy. *Diabetes Metab Res Rev*. 2018;34(4):e2981. doi:10.1002/dmrr.2981
47. Kowalska K, Wilczopolski P, Buławska D, Młynarska E, Rysz J, Franczyk B. The importance of SGLT-2 inhibitors as both the prevention and the treatment of diabetic cardiomyopathy. *Antioxidants (Basel)*. 2022;11(12):2500. doi:10.3390/antiox11122500
48. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin*. 2014;30(6):1109-1119. doi:10.1185/03007995.2014.890925
49. Patel K, Nair A. A literature review of the therapeutic perspectives of sodium-glucose Cotransporter-2 (SGLT2) inhibitor-induced euglycemic diabetic ketoacidosis. *Cureus*. 2022;14(9):e29652. doi:10.7759/cureus.29652
50. Dutta S, Kumar T, Singh S, Ambwani S, Charan J, Varthya SB. Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors: a systematic review and quantitative analysis. *J Family Med Prim Care*. 2022;11(3):927-940. doi:10.4103/jfmpc.jfmpc_644_21
51. Alhemeiri M, Alseddeeqi E. Euglycemic diabetic ketoacidosis after discontinuing SGLT2 inhibitor. *Case Rep Endocrinol*. 2022;2022:4101975. doi:10.1155/2022/4101975
52. Maselli DB, Camilleri M. Effects of GLP-1 and its analogs on gastric physiology in diabetes mellitus and obesity. *Adv Exp Med Biol*. 2021;1307:171-192. doi:10.1007/5584_2020_496
53. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes-state-of-the-art. *Mol Metab*. 2021;46:101102. doi:10.1016/j.molmet.2020.101102
54. Karagiannis T, Avgerinos I, Liakos A, et al. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. *Diabetologia*. 2022;65(8):1251-1261. doi:10.1007/s00125-022-05715-4
55. Lønborg J, Vejlstrup N, Kelbæk H, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;33(12):1491-1499. doi:10.1093/eurheartj/ehr309
56. Kremastiotis G, Handa I, Jackson C, George S, Johnson J. Disparate effects of MMP and TIMP modulation on coronary atherosclerosis and associated myocardial fibrosis. *Sci Rep*. 2021;11(1):23081. doi:10.1038/s41598-021-02508-4
57. Giugliano D, Longo M, Signoriello S, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. *Cardiovasc Diabetol*. 2022;21(1):42. doi:10.1186/s12933-022-01474-z
58. Ma X, Liu Z, Ilyas I, et al. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. *Int J Biol Sci*. 2021;17(8):2050-2068. doi:10.7150/ijbs.59965
59. Arturi F, Succurro E, Miceli S, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. *Endocrine*. 2017;57(3):464-473. doi:10.1007/s12020-016-1166-4
60. Razavi M, Wei YY, Rao XQ, Zhong JX. DPP-4 inhibitors and GLP-1RAs: cardiovascular safety and benefits. *Mil Med Res*. 2022;9(1):45. doi:10.1186/s40779-022-00410-2
61. Liu L, Chen J, Wang L, Chen C, Chen L. Association between different GLP-1 receptor agonists and gastrointestinal adverse reactions: a real-world disproportionality study based on FDA adverse event reporting system database. *Front Endocrinol (Lausanne)*. 2022;13:1043789. doi:10.3389/fendo.2022.1043789
62. Takashima S, Fujita H, Fujishima H, et al. Stromal cell-derived factor-1 is upregulated by dipeptidyl peptidase-4 inhibition and has protective roles in progressive diabetic nephropathy. *Kidney Int*. 2016;90(4):783-796. doi:10.1016/j.kint.2016.06.012
63. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335. doi:10.1056/NEJMoa1305889
64. Enzan N, Matsushima S, Kaku H, et al. Beneficial effects of dipeptidyl Peptidase-4 inhibitors on heart failure with preserved ejection fraction and diabetes. *JACC Asia*. 2023;3(1):93-104. doi:10.1016/j.jacasi.2022.09.015
65. Kanie T, Mizuno A, Takaoka Y, et al. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;10(10):CD013650. doi:10.1002/14651858.CD013650.pub2
66. Doni K, Bühn S, Weise A, et al. Safety of dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Drug Saf*. 2022;13:20420986211072383. doi:10.1177/20420986211072383
67. Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol (Lausanne)*. 2019;10:389. doi:10.3389/fendo.2019.00389
68. Gilbert MP, Pratley RE. GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. *Front Endocrinol (Lausanne)*. 2020;11:178. doi:10.3389/fendo.2020.00178
69. Shirakawa J, Terauchi Y. Potential linkage between dipeptidyl peptidase-4 inhibitor use and the risk of pancreatitis/pancreatic cancer. *J Diabetes Investig*. 2020;11(4):789-791. doi:10.1111/jdi.13192
70. Carnovale C, Mazhar F, Arzenton E, et al. Bullous pemphigoid induced by dipeptidyl peptidase-4 (DPP-4) inhibitors: a pharmacovigilance-pharmacodynamic/pharmacokinetic assessment through an analysis of the vigibase®. *Expert Opin Drug Saf*. 2019;18(11):1099-1108. doi:10.1080/14740338.2019.1668373
71. Galli M, Benenati S, Franchi F, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J*. 2022;43(10):959-967. doi:10.1093/eurheartj/ehab836
72. Li X, Zhang G, Cao X. The function and regulation of platelet P2Y12 receptor. *Cardiovasc Drugs Ther*. 2023;37(1):199-216. doi:10.1007/s10557-021-07229-4
73. Cattaneo M. P2Y12 receptors: structure and function. *J Thromb Haemost*. 2015;13(Suppl 1):S10-S16. doi:10.1111/jth.12952

74. Reiss AB, Grossfeld D, Kasselman LJ, et al. Adenosine and the cardiovascular system. *Am J Cardiovasc Drugs*. 2019;19(5):449-464. doi:10.1007/s40256-019-00345-5
75. Bell RM, Sivaraman V, Kunuthur SP, Cohen MV, Downey JM, Yellon DM. Cardioprotective properties of the platelet P2Y12 receptor inhibitor, cangrelor: protective in diabetics and reliant upon the presence of blood. *Cardiovasc Drugs Ther*. 2015;29(5):415-418. doi:10.1007/s10557-015-6609-2
76. Chen H, Tran D, Yang HC, Nylander S, Birnbaum Y, Ye Y. Dapagliflozin and Ticagrelor have additive effects on the attenuation of the activation of the NLRP3 inflammasome and the progression of diabetic cardiomyopathy: an AMPK-mTOR interplay. *Cardiovasc Drugs Ther*. 2020;34(4):443-461. doi:10.1007/s10557-020-06978-y
77. Ye J, Li L, Wang M, et al. Diabetes mellitus promotes the development of atherosclerosis: the role of NLRP3. *Front Immunol*. 2022;13:900254. doi:10.3389/fimmu.2022.900254
78. Franchi F, James SK, Ghukasyan Lakic T, et al. Impact of diabetes mellitus and chronic kidney disease on cardiovascular outcomes and platelet P2Y12 receptor antagonist effects in patients with acute coronary syndromes: insights from the PLATO trial. *J Am Heart Assoc*. 2019;8(6):e011139. doi:10.1161/JAHA.118.011139
79. Bravo GÁ, Cedeño RR, Casadevall MP, Ramió-Torrentà L. Sphingosine-1-phosphate (S1P) and S1P signaling pathway modulators, from current insights to future perspectives. *Cell*. 2022;11(13):2058. doi:10.3390/cells11132058
80. Davidson SM, Andreadou I, Barile L, et al. Circulating blood cells and extracellular vesicles in acute cardioprotection. *Cardiovasc Res*. 2019;115(7):1156-1166. doi:10.1093/cvr/cvy314
81. Heydari AH, Fathi M, Heydari S, Heidari ME. Advanced glycation end product blocker drugs have a great potential to prevent diabetic cardiomyopathy in an animal model of diabetes mellitus Type-2. *Cardiovasc Ther*. 2022;2022:7014680. doi:10.1155/2022/7014680
82. Zhan B, Xu Z, Zhang Y, et al. Nicorandil reversed homocysteine-induced coronary microvascular dysfunction via regulating PI3K/Akt/eNOS pathway. *Biomed Pharmacother*. 2020;127:110121. doi:10.1016/j.biopha.2020.110121
83. Chen F, Chen ZQ, Zhong GL, Zhu JJ. Nicorandil inhibits TLR4/MyD88/NF-κB/NLRP3 signaling pathway to reduce pyroptosis in rats with myocardial infarction. *Exp Biol Med (Maywood)*. 2021;246(17):1938-1947. doi:10.1177/15353702211013444
84. Wang X, Pan J, Liu D, et al. Nicorandil alleviates apoptosis in diabetic cardiomyopathy through PI3K/Akt pathway. *J Cell Mol Med*. 2019;23(8):5349-5359. doi:10.1111/jcmm.14413
85. Fan Z, Dong J, Mu Y, Liu X. Nesfatin-1 protects against diabetic cardiomyopathy in the streptozotocin-induced diabetic mouse model via the p38-MAPK pathway. *Bioengineered*. 2022;13(6):14670-14681. doi:10.1080/21655979.2022.2066748
86. Luo W, Lin K, Hua J, et al. Schisandrin B attenuates diabetic cardiomyopathy by targeting MyD88 and inhibiting MyD88-dependent inflammation. *Adv Sci (Weinh)*. 2022;9(31):e2202590. doi:10.1002/advs.202202590
87. Liu C, Han Y, Gu X, et al. Paeonol promotes Opa1-mediated mitochondrial fusion via activating the CK2α-Stat3 pathway in diabetic cardiomyopathy. *Redox Biol*. 2021;46:102098. doi:10.1016/j.redox.2021.102098
88. Li H, Shi Y, Wang X, et al. Piceatannol alleviates inflammation and oxidative stress via modulation of the Nrf2/HO-1 and NF-κB pathways in diabetic cardiomyopathy. *Chem Biol Interact*. 2019;310:108754. doi:10.1016/j.cbi.2019.108754
89. Gu X, Shi Y, Chen X, et al. Isoliquiritigenin attenuates diabetic cardiomyopathy via inhibition of hyperglycemia-induced inflammatory response and oxidative stress. *Phytomedicine*. 2020;78:153319. doi:10.1016/j.phymed.2020.153319
90. Zhou Y, Suo W, Zhang X, et al. Targeting epigenetics in diabetic cardiomyopathy: therapeutic potential of flavonoids. *Biomed Pharmacother*. 2023;157:114025. doi:10.1016/j.biopha.2022.114025
91. Wu S, Zhu J, Wu G, et al. 6-Gingerol alleviates Ferroptosis and inflammation of diabetic cardiomyopathy via the Nrf2/HO-1 pathway. *Oxid Med Cell Longev*. 2022;2022:3027514. doi:10.1155/2022/3027514
92. Sims EK, Carr ALJ, Oram RA, DiMeglio LA, Evans-Molina C. 100 years of insulin: celebrating the past, present and future of diabetes therapy. *Nat Med*. 2021;27(7):1154-1164. doi:10.1038/s41591-021-01418-2
93. Aon MA, Tocchetti CG, Bhatt N, Paolocci N, Cortassa S. Protective mechanisms of mitochondria and heart function in diabetes. *Antioxid Redox Signal*. 2015;22(17):1563-1586. doi:10.1089/ars.2014.6123
94. Cortassa S, Caceres V, Tocchetti CG, et al. Metabolic remodelling of glucose, fatty acid and redox pathways in the heart of type 2 diabetic mice. *J Physiol*. 2020;598(7):1393-1415. doi:10.1113/JP276824
95. Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. *Nat Rev Endocrinol*. 2017;13(7):385-399. doi:10.1038/nrendo.2017.39
96. Abdulmalek SA, Balbaa M. Synergistic effect of nano-selenium and metformin on type 2 diabetic rat model: diabetic complications alleviation through insulin sensitivity, oxidative mediators and inflammatory markers. *PLoS One*. 2019;14(8):e0220779. doi:10.1371/journal.pone.0220779
97. Feng J, Wang X, Ye X, et al. Mitochondria as an important target of metformin: the mechanism of action, toxic and side effects, and new therapeutic applications. *Pharmacol Res*. 2022;177:106114. doi:10.1016/j.phrs.2022.106114
98. Kathuria D, Raul AD, Wanjari P, Bharatam PV. Biguanides: species with versatile therapeutic applications. *Eur J Med Chem*. 2021;219:113378. doi:10.1016/j.ejmech.2021.113378
99. Yang F, Qin Y, Wang Y, et al. Metformin inhibits the NLRP3 Inflammasome via AMPK/mTOR-dependent effects in diabetic cardiomyopathy. *Int J Biol Sci*. 2019;15(5):1010-1019. doi:10.7150/ijbs.29680
100. Larsen AH, Jessen N, Nørrelund H, et al. A randomised, double-blind, placebo-controlled trial of metformin on myocardial efficiency in insulin-resistant chronic heart failure patients without diabetes. *Eur J Heart Fail*. 2020;22(9):1628-1637. doi:10.1002/ejhf.1656
101. Yang Z, Wang M, Zhang Y, et al. Metformin ameliorates diabetic cardiomyopathy by activating the PK2/PKR pathway. *Front Physiol*. 2020;11:425. doi:10.3389/fphys.2020.00425
102. Tu MM, Lee FYF, Jones RT, et al. Targeting DDR2 enhances tumor response to anti-PD-1 immunotherapy. *Sci Adv*. 2019;5(2):aav2437. doi:10.1126/sciadv.aav2437
103. Elkamhawy A, Lu Q, Nada H, Woo J, Quan G, Lee K. The journey of DDR1 and DDR2 kinase inhibitors as rising stars in the fight against cancer. *Int J Mol Sci*. 2021;22(12):6535. doi:10.3390/ijms22126535
104. Titus AS, Ushakumary MG, Venugopal H, Wang M, Lakatta EG, Kailasam S. Metformin attenuates Hyperglycaemia-stimulated pro-fibrotic gene expression in adventitial fibroblasts via inhibition of Discoidin domain receptor 2. *Int J Mol Sci*. 2022;24(1):585. doi:10.3390/ijms24010585
105. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the diabetes prevention program outcomes study. *Diabetes Care*. 2012;35(4):731-737. doi:10.2337/dc11-1299
106. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. *Int J Mol Sci*. 2020;21(5):1835. doi:10.3390/ijms21051835

107. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (improved reduction of outcomes: Vytorin efficacy international trial). *Circulation*. 2018;137(15):1571-1582. doi:10.1161/CIRCULATIONAHA.117.030950
108. Sarkar S, Orimoloye OA, Nass CM, Blumenthal RS, Martin SS. Cardiovascular risk heterogeneity in adults with diabetes: selective use of coronary artery calcium in statin use decision-making. *J Gen Intern Med*. 2019;34(11):2643-2647. doi:10.1007/s11606-019-05266-2
109. Ray KK, Colhoun HM, Szarek M, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(8):618-628. doi:10.1016/S2213-8587(19)30158-5
110. Carillion A, Feldman S, Na N, et al. Atorvastatin reduces β-adrenergic dysfunction in rats with diabetic cardiomyopathy. *PloS One*. 2017;12(7):e0180103. doi:10.1371/journal.pone.0180103
111. Liberale L, Carbone F, Camici GG, Montecucco F. IL-1β and statin treatment in patients with myocardial infarction and diabetic cardiomyopathy. *J Clin Med*. 2019;8(11):1764. doi:10.3390/jcm8111764
112. Auer J, Sinzinger H, Franklin B, Berent R. Muscle- and skeletal-related side-effects of statins: tip of the iceberg? *Eur J Prev Cardiol*. 2016;23(1):88-110. doi:10.1177/2047487314550804
113. Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. *Circ Res*. 2019;124(1):121-141. doi:10.1161/CIRCRESAHA.118.311371
114. Akhtar H, Al Sudani H, Hussein M, Farhan MUN, Elkholy K. Effects of renin-angiotensin-aldosterone system inhibition on left ventricular hypertrophy, diastolic function, and functional status in patients with hypertrophic cardiomyopathy: a systematic review. *Cureus*. 2022;14(7):e26642. doi:10.7759/cureus.26642
115. Mascolo A, di Mauro G, Cappetta D, et al. Current and future therapeutic perspective in chronic heart failure. *Pharmacol Res*. 2022;175:106035. doi:10.1016/j.phrs.2021.106035
116. Thomas CM, Yong QC, Rosa RM, et al. Cardiac-specific suppression of NF-κB signaling prevents diabetic cardiomyopathy via inhibition of the renin-angiotensin system. *Am J Physiol Heart Circ Physiol*. 2014;307(7):H1036-H1045. doi:10.1152/ajpheart.00340
117. Zhao K, Xu T, Mao Y, et al. Alamandine alleviated heart failure and fibrosis in myocardial infarction mice. *Biol Direct*. 2022;17(1):25. doi:10.1186/s13062-022-00338-6
118. Rösen R, Rump AF, Rösen P. The ACE-inhibitor captopril improves myocardial perfusion in spontaneously diabetic (BB) rats. *Diabetologia*. 1995;38(5):509-517. doi:10.1007/BF00400718
119. Riccio E, Capuano I, Buonanno P, et al. RAAS inhibitor prescription and hyperkalemia event in patients with chronic kidney disease: a single-center retrospective study. *Front Cardiovasc Med*. 2022;9:824095. doi:10.3389/fcvm.2022.824095
120. Garlo KG, Bates DW, Seger DL, Fiskio JM, Charytan DM. Association of changes in creatinine and potassium levels after initiation of renin angiotensin aldosterone system inhibitors with emergency department visits, hospitalizations, and mortality in individuals with chronic kidney disease. *JAMA Netw Open*. 2018;1(7):e183874. doi:10.1001/jamanetworkopen.2018.3874
121. Dransfield MT, McAllister DA, Anderson JA, et al. β-Blocker therapy and clinical outcomes in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. An observational substudy of SUMMIT. *Ann Am Thorac Soc*. 2018;15(5):608-614. doi:10.1513/AnnalsATS.201708-626OC
122. Zheng W, Li D, Gao X, Zhang W, Robinson BO. Carvedilol alleviates diabetic cardiomyopathy in diabetic rats. *Exp Ther Med*. 2019;17(1):479-487. doi:10.3892/etm.2018.6954
123. Torp-Pedersen C, Metra M, Charlesworth A, et al. Scherhag a; COMET investigators. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the carvedilol or metoprolol European trial (COMET). *Heart*. 2007;93(8):968-973. doi:10.1136/hrt.2006.092379
124. Paolillo S, Dell'Aversana S, Esposito I, Poccia A, Perrone FP. The use of β-blockers in patients with heart failure and comorbidities: doubts, certainties and unsolved issues. *Eur J Intern Med*. 2021;88:9-14. doi:10.1016/j.ejim.2021.03.035
125. Burnier M, Bakris G, Williams B. Redefining diuretics use in hypertension: why select a thiazide-like diuretic? *J Hypertens*. 2019;37(8):1574-1586. doi:10.1097/HJH.0000000000002088
126. Liu W, Gong W, He M, et al. Spironolactone protects against diabetic cardiomyopathy in Streptozotocin-induced diabetic rats. *J Diabetes Res*. 2018;2018:9232065. doi:10.1155/2018/9232065
127. Rahhal A, Najim M, Abusweireh A, et al. A comparative study of safety outcomes of sodium glucose Cotransporter-2 inhibitors and loop diuretics among diabetic patients using real-world data. *Curr Probl Cardiol*. 2022;47(10):100995. doi:10.1016/j.cpcardiol.2021.100995
128. Islam MS. The art and science of using diuretics in the treatment of heart failure in diverse clinical settings. *Adv Exp Med Biol*. 2018;1067:47-65. doi:10.1007/5584_2018_182
129. Li J, Richmond B, Cluntun AA, et al. Cardiac gene therapy treats diabetic cardiomyopathy and lowers blood glucose. *JCI Insight*. 2023;8(18):e166713. doi:10.1172/jci.insight.166713
130. Parim B, Sathibabu Uddandrao VV, Saravanan G. Diabetic cardiomyopathy: molecular mechanisms, detrimental effects of conventional treatment, and beneficial effects of natural therapy. *Heart Fail Rev*. 2019;24(2):279-299. doi:10.1007/s10741-018-9749-1
131. da Silva JS, Gonçalves RGJ, Vasques JF, et al. Mesenchymal stem cell therapy in diabetic cardiomyopathy. *Cell*. 2022;11(2):240. doi:10.3390/cells11020240
132. Kim AH, Jang JE, Han J. Current status on the therapeutic strategies for heart failure and diabetic cardiomyopathy. *Biomed Pharmacother*. 2022;145:112463. doi:10.1016/j.biopha.2021.112463
133. Dannenberg L, Weske S, Kelm M, Levkau B, Polzin A. Cellular mechanisms and recommended drug-based therapeutic options in diabetic cardiomyopathy. *Pharmacol Ther*. 2021;228:107920. doi:10.1016/j.pharmthera.2021.107920

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